

## NUT BIOACTIVES IN COGNITIVE IMPAIRMENT: MECHANISMS, COMPARISONS, AND RESEARCH GAPS

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### Abstract

Over 55 million individuals globally experience cognitive impairment. This condition arises from factors such as oxidative stress, neuroinflammation, the aggregation of proteins like amyloid-beta and tau, as well as synaptic dysfunction. Current medications, including cholinesterase inhibitors, provide only symptomatic relief without changing the course of the disease. This review examines neuroprotective bioactive compounds sourced from tree nuts specifically walnuts, pecans, almonds, and pistachios. It includes a discussion of phenolic such as gallic and ellagic acids, flavonoids like quercetin and kaempferol, tocopherols, polyunsaturated fatty acids including  $\alpha$ -linolenic acid, and peptides. These target key pathways: ROS scavenging/Nrf2 activation for antioxidants; NF- $\kappa$ B/cytokine inhibition for anti-inflammation; cholinesterase blockade; BDNF for synaptic plasticity. Walnuts have the best evidence (WAHA trial: better memory and executive function); pecans have the most antioxidants (ORAC 17,940  $\mu$ mol TE/100g); and almonds have the most vitamin E. Analytical tools like HPLC-MS and docking connect profiles to effects, but there are still gaps in standardization, bioavailability, long-term trials, and data that doesn't come from walnuts. Nut bioactives hold potential for enhancing cognitive health by addressing various aspects. Future studies must identify the most effective formulations and evaluate them in clinical environment.

**Keywords:** *Cognitive impairment, Neuroprotection, Nut bioactives, Oxidative stress and Neuroinflammation, Neuroplasticity.*

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Received: 03/04/2026

Revised: 05/05/2026

Accepted: 05/05/2026

DOI: <http://doi.org/10.66204/GJPSR-778-2026-2-5-6>

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### How to Cite

Yeasmin L, Khan MSA, Bhandari R, Raj R, Mollah A, Dubey M. Nut bioactives in cognitive impairment: mechanisms, comparisons, and research gaps. *Global Journal of Pharmaceutical and Scientific Research*. 2026, ISSN: 3108-0103. 2026;2(5):788–810. ISSN: 3108-0103. <http://doi.org/10.66204/GJPSR-778-2026-2-5-6>

## **1. INTRODUCTION**

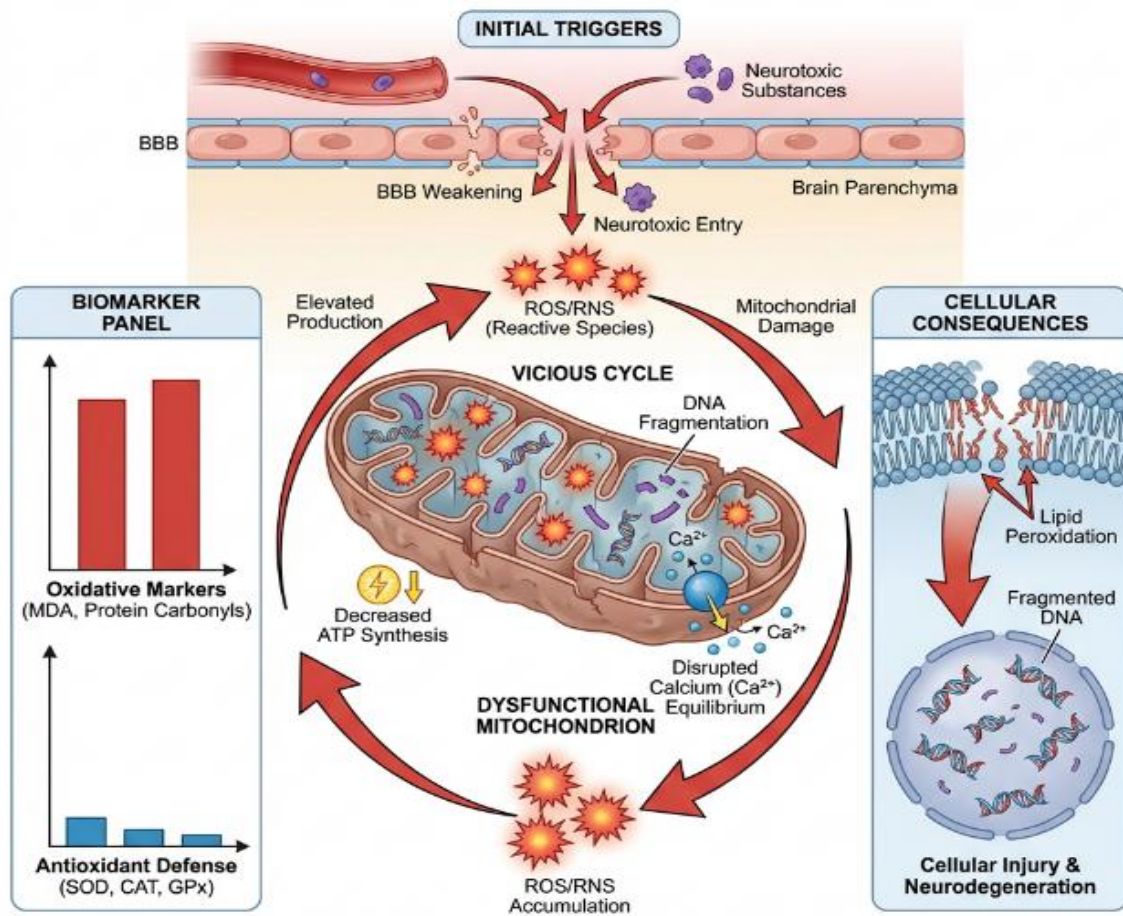
Cognitive impairment encompasses various neurological disorders that gradually hinder one's ability to remember information, make decisions, and regulate behavior. It presents a major risk to global health, affecting around 55 million people across the globe. Protein aggregation, oxidative stress, neuroinflammation, and synaptic dysfunction are intricate processes that may contribute to cognitive decline. All of these factors damage neurons, hindering their ability to perform their functions effectively. Most of the medications available today, such as NMDA receptor antagonists and cholinesterase inhibitors, primarily address symptoms. They do not prevent the progression of the disease or resolve its underlying causes (Ahmed & Braidy, 2021; Howes et al., 2020; Okello & Mather, 2020).

Nutritional neuroscience has demonstrated that bioactive compounds found in food play a crucial role in maintaining brain health and protection (Murray et al., 2024; Howes et al., 2020). People are starting to think that tree nuts are a healthy food because they are full of phytochemicals (de Rus Jacquet et al., 2023; Ghasemzadeh Rahbardar & Hosseinzadeh, 2024; Chauhan & Chauhan, 2020).

Bioactive compounds present in nuts, including phenolic acids, flavonoids, tocopherols, polyunsaturated fatty acids, and bioactive peptides, are believed to offer protection to the brain (Theodore et al., 2021; Gorji et al., 2018; Bolling et al., 2010). Epidemiological studies show negative relationships between nut consumption and cognitive decline, while mechanistic research reveals that nuts can influence key pathways linked to neurodegeneration. These findings highlight the importance of investigating bioactive compounds that are extracted from nuts (Ghasemzadeh Rahbardar & Hosseinzadeh, 2024; Chauhan & Chauhan, 2020).

This review offers an in-depth examination of the current understanding of nut bioactives and their relationship with cognitive impairment. It examines the effectiveness of these methods, compare them with alternative approaches, analyzes the techniques employed in their study, and highlights the shortcomings present in the existing research . This review brings together findings to clarify the neuroprotective effects of certain compounds found in nuts and to highlight important areas for the future research and therapeutic development.

## 2. Pathogenesis of Cognitive Impairment



**Fig 1: Mitochondrial Dysfunction and Oxidative Stress**

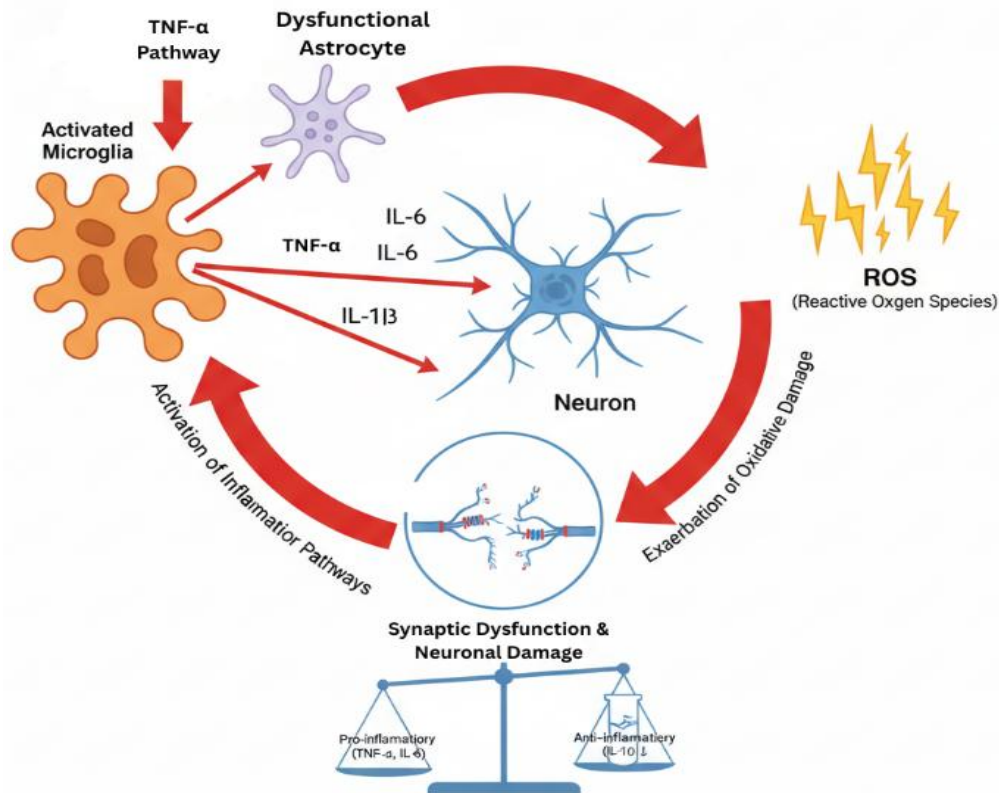
Oxidative stress can affect the central nervous system more than other organs since it requires substantial oxygen, contains significant lipids, and possesses limited antioxidants (Khalili et al., 2022; Hassan et al., 2022).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) get accumulated over time, specially during adverse conditions. causing cells to decompose lipids, proteins, and DNA, which damages them. Low levels of ATP have shown mitochondrial problems as a big part of neurodegeneration caused by oxidative stress. An imbalance in calcium levels, together with an increase in the production of reactive oxygen species (ROS), trigger a continuous cycle of cellular damage that perpetuates indefinitely (Fischer & Maier, 2015; Yeni et al., 2025).

Researchers have found that people with Alzheimer's disease and other neurodegenerative diseases have a lot more oxidative stress markers in their brains. Malondialdehyde (MDA) and protein carbonyls represent two of these indicators (Xiang et al., 2022; Gurung et al.,

2024; d'Avila et al., 2018). When antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are present in lower amounts, cells become less capable of defending themselves (Gurung et al., 2024; Zhang et al., 2020; d'Avila et al., 2018). Oxidative stress harms the blood-brain barrier, allowing neurotoxic substances to enter the brain tissue and exacerbating neuronal damage.

### 3. Neuroinflammation and an Imbalance of Cytokines

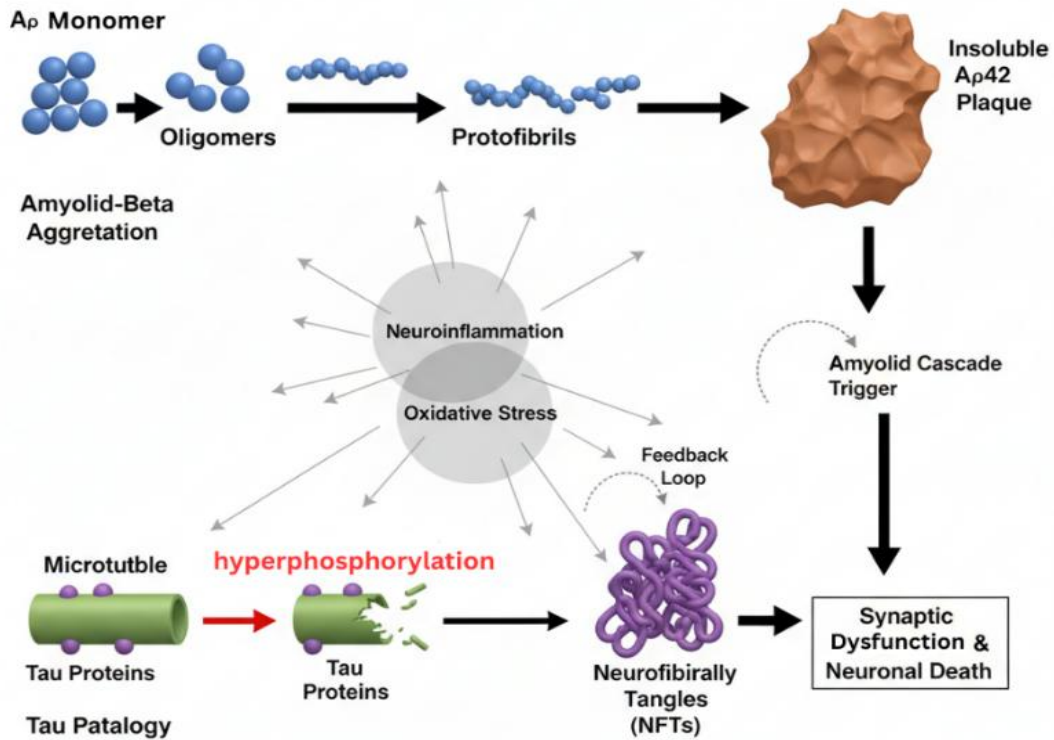


**Fig 2: Pathways of Chronic Neuroinflammation and Oxidative Stress**

Chronic neuroinflammation greatly worsens cognitive impairments in individuals. This occurs when microglia become activated, leading to impaired function of astrocytes and resulting in the uncontrolled production of cytokines. When microglia become activated, they secrete pro-inflammatory substances such as interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ). These things could hurt neurons and mess up how synapses work (d'Avila et al., 2018). The nuclear factor kappa B (NF- $\kappa$ B) signaling pathway plays a crucial role in regulating inflammation within the body. If not adequately activated, it could prolong neuroinflammation (Kim et al., 2024).

Oxidative stress and neuroinflammation are interconnected processes. Reactive oxygen species (ROS) trigger the inflammatory response, while inflammatory mediators relieve oxidative damage. This initiates a feedback loop that accelerates the decline of cognitive and neurological functions. In neurodegenerative diseases, the concentrations of anti-

inflammatory cytokines such as interleukin-10, are frequently diminished, initiating the imbalance that starting pro-inflammatory responses.



**Fig 3: Hyperphosphorylation of tau and the aggregation of amyloid-beta**

Proteins frequently misfolded and aggregate in significant neurodegenerative disorders. Amyloid-beta ( $A\beta$ ) plaques and neurofibrillary tangles made of tau protein that has been hyperphosphorylated are two things that are common in Alzheimer's disease.  $A\beta$  peptides, especially the  $A\beta$ 42 isoform, gradually accumulate from soluble monomers to oligomers, then to protofibrils, and finally lead to the formation of insoluble plaques. This cluster of cells diminishes the effectiveness of synapses and accelerates neuronal death (Yin et al., 2020). Excessive phosphorylation of tau protein leads to the formation of neurofibrillary tangles and destabilizes the microtubules within cells. This diminishes the strength of the cells and complicates the ability of axons to assist with transport (Ahmed & Braidy, 2021).

The amyloid cascade hypothesis suggests that the buildup of  $A\beta$  triggers a series of harmful events, including tau pathology, neuroinflammation, and oxidative stress. However, recent findings indicate that these disease mechanisms are more complex than previously thought. For example, tau pathology might arise independently and affect  $A\beta$  accumulation through feedback mechanisms (Ahmed & Braidy, 2021). Oxidative stress and inflammation play crucial roles in the processes that result in protein aggregation. This illustrates the interconnectedness of the processes that lead to neurodegeneration.

## **4. Nut-Derived Bioactive Mechanism**

### **4.1 Pecan (*Carya illinoensis*)**

Pecans rank among the tree nuts that possess the most potent antioxidant properties. The elevated concentrations of flavonoids and phenolic acids significantly contribute to their benefits for brain health (Chauhan & Chauhan, 2020). Tests measuring the oxygen radical absorbance capacity (ORAC) indicate that pecans are rich in gallic acid, ellagic acid, catechins, and proanthocyanidins. These substances are particularly effective at combating free radicals (Chauhan & Chauhan, 2020; Bolling et al., 2010). Recent metabolomics research has discovered urolithin metabolites in human plasma following the consumption of pecans. This suggests that ellagitannin compounds may protect the brain (Chauhan & Chauhan, 2020).

Pecans are rich in  $\gamma$ -tocopherol, a form distinct from  $\alpha$ -tocopherol. It may be more effective against reactive species containing nitrogen (Bolling et al., 2010). Pecans possess a distinctive fatty acid composition, characterized by a high concentration of oleic acid and a smaller amount of  $\alpha$ -linolenic acid (Bolling et al., 2010). This aids in preventing the breakdown of membranes and signals the body to combat inflammation. The current clinical evidence does not adequately support the assertion that eating pecans enhances cognitive function, posing a significant challenge for translational research (Chauhan & Chauhan, 2020).

### **4.2 Walnut (*Juglans regia*)**

Numerous studies have examined walnuts to determine their impact on brain health in comparison to other types of nuts. A substantial body of convincing evidence from both preclinical and clinical studies shows that they offer protective benefits for the brain (Moon et al., 2022; Rajaram et al., 2017; Zhang et al., 2023). Walnuts are an excellent source of  $\alpha$ -linolenic acid (ALA), a plant-based omega-3 fatty acid. ALA helps in maintaining the flexibility of cell membranes and plays an important role in signaling pathways that inhibit inflammation. Walnuts contain a variety of phenolic compounds, including ellagic acid, protocatechuic acid, ferulic acid, quercetin, kaempferol (de Rus Jacquet et al., 2023; Rajaram et al., 2017; Demirel et al., 2024).

Clinical studies have shown that the intake of walnuts can enhance memory, reaction time, and executive function in both healthy adults and older individuals. Research investigating the short-term impact of eating a significant amount of walnuts for breakfast suggests that it

can quickly boost cognitive function and maintain this enhancement over the course of the day. This states that the body can quickly absorb the active compounds (Rajaram et al., 2017; Tan et al., 2022). Studies have also shown that peptides taken from walnuts, especially those are high in arginine, protect neurons by altering the neurotransmitters and changing the activity of antioxidant enzymes (Moon et al., 2022; Raghu et al., 2023).

Research utilizing transgenic animal models of Alzheimer's disease suggests that diets rich in walnuts notably improve memory, learning, motor coordination, and behaviors associated with anxiety. These diets also contribute to reducing indicators of oxidative stress and neuroinflammation (Zhang et al., 2023; Ghasemzadeh Rahbardar & Hosseinzadeh, 2024; Raghuvanshi et al., 2025). The Walnuts and Healthy Aging (WAHA) study was an extensive clinical trial conducted over two years of time, examining the impact of walnut consumption on the cognitive and ocular health of older adults (Guo & Rezaei, 2024; Dubey et al., 2024).

#### **4.3 Almonds (*Prunus dulcis*)**

Almonds are shown to provide better source of protein, fiber, and vitamin E ( $\alpha$ -tocopherol). They also contain lots of phenolic compounds, including flavonoids and phenolic acids (Lee et al., 2025; Topiya & Pandya, 2024; Stevens-Barrón et al., 2019). Almonds contain phenolic acids such as quercetin, kaempferol, and isorhamnetin, which combat free radicals. But these chemicals are not as potent as those found in walnuts and pecans (Lee et al., 2025; Bolling et al., 2010). Regular consumption of almonds has been associated with enhanced heart health and improved metabolism. Additionally, this may benefit brain health by promoting better blood circulation (Lee et al., 2025).

In silico molecular docking studies suggest that sweet almond oil has compounds that could be useful for treating diseases and that can interact with the brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) pathways. This suggests that they might protect the brain. There is insufficient direct clinical evidence demonstrating that consuming almonds benefits brain health, indicating a need for more targeted intervention studies (Lee et al., 2025; Topiya & Pandya, 2024).

#### **4.4 Pistachio (*Pistacia vera*)**

Pistachios possess unique phytochemical profiles that distinguish them from other nuts. The colored sections of the nuts, for example, are rich in proanthocyanidins, anthocyanins, and various phenolic acids. Tree nuts can fight free radicals because they are full of both lipophilic and hydrophilic antioxidant compounds (Bolling et al., 2010; Akintorinwa et al., 2025). Research involving human participants has demonstrated that consuming pistachios can increase antioxidant levels and reduce oxidative stress.

Not much is known about how pistachios affect the brain, but they are very good for you, which could mean they protect it (Chauhan & Chauhan, 2020; Bolling et al., 2010). Lutein and zeaxanthin are essential nutrients that promote retinal health. Pistachios are an excellent source of both. The nerves and blood vessels linking the retina to the brain resemble those found in pistachios. This suggests that these nuts could also benefit your brain health.

**Table 1: Key phytochemical difference across major nuts**

<b>Nut (per 100 gm)</b>	<b>Total phenolics ( mg gallic acid eq.)</b>	<b>Flavonoids(mg)</b>	<b>Vitamin E ( <math>\alpha</math>-tocopherol, mg)</b>	<b>Distinctive features</b>
Walnut	1,625	28	20.8	Highest phenolics;rich in Ala; quercetin & kaempferol derivatives
Pecan	1,284	34	1.4	Very high flavonoids ; rich in gallic ; ellagic acid , catechins, proantharocyanidins; $\gamma$ -tocopherol
Pistachio	1,160	24	2.9	Rich in proanthocyanidins, anthocyanins; lutein and zeaxanthin
Almond	187	14	25.6	Lowest phenolics ; highest vitamin E ; quercetin & isorhamnetin

## 5. Key Bioactive and Their Roles

### 5.1 Flavonoids, tocopherols, and polyunsaturated fatty acids (PUFAs)

The neuroprotective benefits of nuts stem from the combined effects of different bioactive compounds. Gallic, ellagic, protocatechuic, and ferulic acids represent a category of phenolic compounds recognized for their potent antioxidant characteristics (de Rus Jacquet et al.,

2023; Ghasemzadeh Rahbardar & Hosseinzadeh, 2024; Howes et al., 2020). These compounds can be obtained in various forms. Certain work by eliminating reactive oxygen species (ROS), sequestering metals, and enhancing the efficiency of the body's natural antioxidant systems (de Rus Jacquet et al., 2023; Baciu et al., 2023; Balakrishnan et al., 2021). Flavonoids such as quercetin, kaempferol, and catechins protect the brain by altering the pathways that regulate cell survival, inflammation, and synaptic plasticity (Ahmed & Braidy, 2021; Baciu et al., 2023; Gregory et al., 2021). Tocopherols and tocotrienols play a crucial role in safeguarding neuronal membranes against lipid peroxidation. Different isoforms serve distinct biological functions. In nuts,  $\gamma$ -tocopherol protects better against nitrogen-based reactive species than  $\alpha$ -tocopherol. Polyunsaturated fatty acids, especially  $\alpha$ -linoleic acid found in walnuts, enhance membrane function and promote the production of certain pro-resolving mediators that help reduce neuroinflammation (Howes et al., 2020).

**Table 2: Key metabolic pathways targeted by nut bioactives**

<b>Mechanism</b>	<b>Main bioactive involved</b>	<b>Nuts where especially relevant</b>	<b>Mechanistic details</b>
Antioxidant (ROS scavenging, Nrf2)	Phenolic acids, flavonoids, tocopherols	All strongest in walnuts & pecans	Direct ROS scavenging, metal chelation, Nrf2 activation, increase antioxidant enzyme
Anti-inflammatory (NF- $\kappa$ B, cytokines)	Phenolics, PUFAs (ALA)	Walnuts, pecans, pistachios	Inhibits NF- $\kappa$ B, reduce TNF- $\alpha$ , Il-6, cox-2, iNOs; promotes anti-inflammatory mediators
Cholinesterase inhibition	Phenolic compounds	Especially walnut phenolics/peptides	Inhibit AChE/BChE, prolong synaptic acetylcholine
Synaptic plasticity,	Peptides, certain oils	Walnuts; potentials in	Increases

BDNF	& phenolics	almonds	BNDF/TrkB signaling, neurogenesis, improved memory/learning
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## **5.2 Antioxidants, Anti-inflammatory, and Neuroprotective Mechanism**

There are many ways in which nut bioactives protect the brain, and they all work together to change important pathological processes that is the main cause of cognitive impairment (de Rus Jacquet et al., 2023; Ghasemzadeh Rahbardar & Hosseinzadeh, 2024; Demirel et al., 2024). Some act as antioxidant which protect neural components from oxidative damage include the elimination of reactive oxygen species (ROS), the chelation of metal ions, and the inhibition of lipid peroxidation (Bolling et al., 2010; Balakrishnan et al., 2021). These chemicals also stimulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, increasing the body's natural antioxidant defenses and increasing the production of antioxidant enzymes (Kim et al., 2024; Yin et al., 2020; Gregory et al., 2021).

Nut bioactives diminish the generation of pro-inflammatory cytokines, inhibit NFκB signaling pathways, and promote the synthesis of anti-inflammatory mediators. Eating nuts has been demonstrated to increase the levels of anti-inflammatory cytokines in the bloodstream, while simultaneously reducing the levels of inflammatory markers such as TNF-α, IL-6, and C-reactive protein. Nut bioactives reduce neuroinflammation and alter the functioning of microglia, rendering them anti-inflammatory within the central nervous system (Demirel et al., 2024).

## **6. Mechanism Insight**

### **6.1 ROS scavenging**

Nut bioactives serve as natural antioxidants by fighting with reactive oxygen and nitrogen species through various mechanisms. Phenolic compounds donate hydrogen atoms or electrons to free radicals, increasing their stability and hindering oxidative chain reactions that could probably affect the biological components. The antioxidant qualities of flavonoids and their ability to interact with different reactive species depend on their structural features, such as the presence of hydroxyl groups and the arrangement of conjugated rings (Baciu et al., 2023; Balakrishnan et al., 2021).

Metal chelation serves as the primary mechanism through which antioxidants exert their effects. The Fenton process generates hydroxyl radicals, which initiate a high level of

reactivity. Copper and iron are among the most significant transition metals that help this reaction. Flavonoids and phenolic acids make stable complexes with metal ions, which stops these metal ions from taking part in oxidative reactions. Chelating metals is crucial, excess of these elements induce oxidative stress in neurodegenerative diseases (Baciu et al., 2023; Balakrishnan et al., 2021).

## **6.2 Inhibition of Neuroinflammatory Pathway**

Nut bioactives primarily influence neuroinflammation is by blocking NF- $\kappa$ B. Phenolic compounds hinder the activation of NF- $\kappa$ B by blocking transcription factors from moving into the nucleus, which in turn promotes the breakdown of proteins vital for this process (Kim et al., 2024). Consequently, the expression levels of pro-inflammatory genes, including cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and various cytokines, are reduced.

Altering the mitogen-activated protein kinase (MAPK) pathways, such as the p38 MAPK and c-Jun N-terminal kinase (JNK) pathways, can also aid in diminishing inflammation. These pathways regulate the body's response to inflammation. Nut bioactives also help in increasing neuroinflammation by altering the balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) microglia phenotypes (Demirel et al., 2024).

## **6.3 Cholinesterase Inhibition**

Numerous compounds present in nuts have shown the ability to inhibit cholinesterase, thereby enhancing cholinergic neurotransmission and subsequently boosting cognitive performance (Bolling et al., 2010; Stevens-Barrón et al., 2019; Esselun et al., 2021). In vitro research has demonstrated that phenolic compounds and flavonoids derived from nuts can inhibit butyrylcholinesterase and acetylcholinesterase in a manner akin to that of established pharmaceutical inhibitors. This mechanism stops acetylcholine from breaking down by attaching to the active site of cholinesterase. Consequently, neurotransmitters remain in the synaptic cleft for an extended period (Howes et al., 2020; Esselun et al., 2021; Reza-Zaldívar & Jacobo-Velázquez, 2023).

Molecular docking studies have shown that phenolic compounds found in nuts engage with the active sites of cholinesterase in unique ways. The hydrogen bonding forces and hydrophobic interactions that facilitate these connections are crucial for maintaining the stability of inhibitor-enzyme complexes. These interactions could enhance disease treatment, similar to the methods used by approved cholinesterase inhibitors, such as donepezil and galantamine (de Rus Jacquet et al., 2023; Piva et al., 2024; Theodore et al., 2021).

## **6.4 Modulation of Neurotransmitters and Synaptic Plasticity**

Bioactive compounds found in nuts influence various neurotransmitter systems associated with cognitive function, including cholinergic systems (Moon et al., 2022; Raghu et al., 2023). Studies indicate that peptides derived from walnuts alter the functioning of serotonergic and dopaminergic signaling pathways, leading to enhancements in mood and cognitive performance. These effects regulate the production, release, and responsiveness of neurotransmitter receptors .

Nuts are rich in bioactive compounds that increases the production of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), and activate the pathways related with these factors. This enhances the flexibility of synapses, which is a primary mechanism through which cognitive benefits are realized. BDNF signaling via tropomyosin receptor kinase B (TrkB) increases memory and learning via strengthening synapses, preserving neuronal health, and increasing brain plasticity. Eating nuts has shown to activates certain genes that are important for neurogenesis and how synapses work (Zhang et al., 2023; Raghu et al., 2023; Lee et al., 2025).

## **7. Comparative Analysis of Nuts**

### **7.1 Phytochemical Profiles**

Researchers have carried out thorough analyses of the phytochemical composition in various types of nuts, revealing significant differences that influence their neuroprotective effectiveness. Walnuts contain the highest concentration of phenolic compounds, boasting 1,625 mg of gallic acid equivalents for every 100 grams. Pecans rank second, providing 1,284 mg of nutrients per 100 g, while pistachios follow closely in third place with 1,160 mg per 100 g. Almonds, in contrast, contain just 187 mg of phenolic compounds per 100 grams, which is significantly lower. Some nuts have more phytochemicals than others because of how they are made and their genes (Chauhan & Chauhan, 2020; Bolling et al., 2010).

Almonds contain a moderate quantity of flavonoids, providing 14 mg for every 100 grams. Pecans lead the way, containing 34 mg per 100 grams, while walnuts follow closely behind with 28 mg per 100 grams. Pistachios, in contrast, contain the lowest amount, offering just 24 mg per 100 grams. Pistachios are rich in anthocyanin and proanthocyanidins, whereas pecans contain a significant amount of catechins and proanthocyanidins. Almonds are high in quercetin and isorhamnetin, while walnuts are high in quercetin and kaempferol derivatives.

Almonds are rich in  $\alpha$ -tocopherol, containing 25.6 mg per 100 grams, whereas walnuts offer a moderate level with 20.8 mg per 100 grams. Pistachios and pecans, in contrast, contain lower amounts, with 2.9 mg and 1.4 mg per 100 grams, respectively. Pecans and pistachios contain

varying levels of tocopherol, which influences living organisms in distinct manners (de Rus Jacquet et al., 2023; Bolling et al., 2010).

## **7.2 Antioxidant Capacity**

Standardized tests measuring antioxidant capacity indicate that certain nuts are more effective at neutralizing free radicals compared to others. Pecans exhibited the highest oxygen radical absorbance capacity (ORAC) values, measuring 17,940  $\mu\text{mol}$  Trolox equivalents per 100 grams. There were 13,541 walnuts, 7,675 pistachios, and 4,454 almonds remaining after that [18]. The differences illustrate how various compounds function as antioxidants and how they can collaborate to enhance each other's effectiveness. These modifications are also connected to the overall quantity of phenolic compounds. Pecans and walnuts demonstrated a greater ability to neutralize DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals compared to almonds and pistachios. This supports our previous findings (Salis et al., 2025; Gomes et al., 2024).

Research utilizing FRAP (ferric reducing antioxidant power) supports these rankings regarding the effectiveness of various antioxidants. Walnuts and pecans always do well in tests of their antioxidant properties. This suggests that they may represent the most effective sources of neuroprotective compounds.

## **7.3 Evidence in Cognitive Models**

Walnuts have been the subject of thorough research, including studies involving humans, animals, and laboratory experiments (Rajaram et al., 2017; Tan et al., 2022). Conversely, the robustness of the evidence regarding the cognitive advantages of various types of nuts differs significantly. Multiple randomized controlled trials have shown that consuming walnuts improves memory, decision-making, and information processing in both healthy individuals and older adults. Research utilizing transgenic animal models of Alzheimer's disease has consistently shown that diets incorporating walnuts enhance cognitive function and reduce indicators of neuropathology (Raghuvanshi et al., 2025).

Pistachios and pecans possess beneficial phytochemical profiles, yet there is no definitive evidence to suggest that they enhance cognitive function. Researchers have used both computers and people to show that almonds are good for your health. The gap between the potential benefits of antioxidants and the actual outcomes observed in clinical settings highlights the significance of bioavailability, metabolism, and specific molecular pathways in evaluating the effectiveness of treatments (Lim et al., 2024; Carrillo et al., 2025; Arias-Sánchez et al., 2023).

### **Table 3: Antioxidant Capacity Versus Cognitive Evidence by Nuts Types**

Nut	ORAC ( $\mu\text{mol TE}/100\text{ mg}$ )	Antioxidant Ranking	Human/Animal Evidence for Cognition	Key Notes
Pecan	17,940	Highest	No adequate clinical evidence for cognition improvement	Strong antioxidant profiling; urolithin metabolites detected after intake
Walnut	13,541	Very high	Multiple RCTs and animal models show improved memory, reaction time, executive functions	Best overall evidence base (WAHA trial and others)
Pistachio	7,675	Moderate	Very limited, no definitive cognitive data	Human study shows improved antioxidant status and reduced oxidative stress
Almond	4,454	Lowest	Insufficient direct clinical evidence for brain benefits	Strong cardiovascular and metabolic effects; potential indirect brain benefits

#### 7.4 Strength and Limitations

Robust clinical trials, numerous animal studies, and a clear identification of bioactive compounds all indicate that walnuts are beneficial for brain health. It contains a higher amount of  $\alpha$ -linolenic acid compared to other foods, which benefits heart health and exhibits more potent anti-inflammatory properties. It may also improve brain function by sending more blood to the brain through the vascular system. Individuals with tree nut allergies might find it challenging to consume walnuts due to their higher calorie content per serving (Topiya & Pandya, 2024; Dzah, 2023).

While clinical evidence is limited, pecans are rich in phytochemicals and possess significant antioxidant properties, suggesting they could be beneficial for brain health. Our understanding of how the body absorbs and metabolizes peas remains limited due to a lack of sufficient research in these fields (Chauhan & Chauhan, 2020). There is not enough direct evidence to support the assertion that almonds improve brain health, and they contain a lower level of phenolic compounds compared to other foods. But they do have a lot of vitamin E, and research has shown that they are good for your heart (Bolling et al., 2010; Lee et al., 2025). Pistachios are rich in distinctive anthocyanin compounds and particular antioxidants; nonetheless, further investigation is needed to assess their impact on cognitive function.

### 8. Multi-Analytical approaches

#### 8.1 Analytical Techniques for Profiling Bioactive

To discuss the bioactive compounds in nuts, it is essential to understand how to identify and quantify the various phytochemicals present. This requires advanced analytical methods.

High-performance liquid chromatography (HPLC) with diode array detection (DAD) is the most common way to analyze phenolic compounds. DAD is great at separating and measuring different compounds (Gomes et al., 2024; Kang et al., 2023; Shaik et al., 2025; Kim et al., 2025). Ultra-high-performance liquid chromatography (UHPLC) has significantly accelerated the analysis process, enhanced its capability to address complex challenges, and maintained the same level of accuracy as conventional methods (Pandit & Vyas, 2021; Nxumalo et al., 2024).

Liquid chromatography-mass spectrometry (LC-MS) and tandem mass spectrometry (LC-MS/MS) are effective techniques for precisely identifying bioactive compounds (Kang et al., 2023; Shaik et al., 2025). They achieve this by measuring the mass of these compounds and fragmenting them into smaller components for analysis. These techniques assist in identifying novel substances and metabolites that may not be accessible as reference standards. Time-of-flight mass spectrometry (LC-TOF-MS) excels in identifying compounds with exceptional mass accuracy; however, triple quadrupole systems are superior for providing precise quantitative measurements (Carrillo et al., 2025; Kang et al., 2023).

Nuclear magnetic resonance (NMR) spectroscopy serves as a crucial method for determining the structure of individual molecules. It provides extensive details regarding the connections between atoms in molecules and their spatial arrangement. NMR studies, which can be done in one or two dimensions, can give us a full picture of the structure of new bioactive compounds. Gas chromatography-mass spectrometry (GC-MS) is an effective method for identifying fatty acids and volatile compounds present in nuts (Pandit & Vyas, 2021; Nxumalo et al., 2024).

## **8.2 Molecular Docking Studies**

Molecular docking plays a crucial role in medicinal chemistry as it aids in the discovery and enhancement of new pharmaceuticals using computer molecular docking is an effective method to determine how the bioactive compounds found in nuts can alter the proteins, crucial for brain health. Molecular docking studies suggest that phenolic compounds found in nuts could engage with crucial enzymes, including acetylcholinesterase and butyrylcholinesterase, as well as a range of inflammatory mediators (de Rus Jacquet et al., 2023; Piva et al., 2024; Theodore et al., 2021). These computer methods show how some chemicals protect neurons at the molecular level.

For protein-ligand complexes to maintain stability, the presence of hydrogen bonds and hydrophobic interactions is crucial. Studies of docking with walnut phenolic and acetylcholinesterase show that these compounds bind in ways that are similar to those of

known inhibitors. Investigations into inflammatory targets, such as the enzymes lipoxygenase and cyclooxygenase, have revealed promising strategies for reducing inflammation (PTSRK, 2025). Molecular dynamics simulations provide additional support for the docking data by assessing the stability of the complex over time.

When examining docking results, structure-activity relationship (SAR) analysis can identify key structural characteristics that contribute to biological function. This can make natural compounds stronger or make it easier to make synthetic ones. The results obtained from molecular docking require validation through in vitro and in vivo experiments to verify the presence of the anticipated activities (Theodore et al., 2021; Er Demirhan & Demirhan, 2022).

### **8.3 Correlation of Chemical Composition with Biological effects**

When studying natural products, it's important to know how the chemical makeup affects biological activity. You can't tell what a mixture will do just by looking at how its parts act. Using LC-MS and NMR in metabolomics allows for the examination of all parent compounds and their metabolites within living organisms. These studies suggest that the compounds linked to food breakdown and energy transformation might demonstrate heightened activity within the organism compared to their precursor compounds. Certain categories of phytochemicals exhibit a stronger association with antioxidant capacity compared to others. This means that the total amount of phenolic compounds has less of an effect on how well they work as antioxidants than certain molecular structures. Similarly, specific chemicals or metabolites might exhibit anti-inflammatory properties, rather than solely the overall quantity of phytochemicals (Lim et al., 2024; Carrillo et al., 2025).

The way that different foods work together can change how well bioactive substances work and how quickly they are absorbed. Nuts contain protein, fiber, and fat, all of which can influence the body's processes for releasing, absorbing, and metabolizing various substances. This may lead to a discrepancy between the anticipated biological effects and those that are actually observed. To fully harness the healing properties of nut bioactive, it is essential to understand how these matrix interactions function (Arias-Sánchez et al., 2023; Spadaro et al., 2020; Sagu et al., 2021).

## **9. Research Gaps and Future Directions**

### **9.1 Lack of standardized Extract and Dosages**

One of the major challenges in nut bioactive research is the absence of clear guidelines regarding the extraction of these compounds from nuts and the appropriate dosage to consume. Recent studies have used different extraction methods, such as aqueous, ethanoic,

and supercritical fluid extraction, to create different phytochemical profiles and biological activities. Determining the optimal dosage schedules from research data is challenging due to the lack of standardization (Arias-Sánchez et al., 2023; Donno et al., 2020).

The concentration of bioactive compounds in nuts can differ among batches due to variables such as seasonality, origin, processing techniques, and storage conditions. This diversity complicates the creation of standardized extracts for medical applications. To promote the advancement of nut-based therapies for medical applications, it is essential to establish quality control measures and standardization protocols.

We remain uncertain about the optimal method for adjusting the dosage, despite research examining both short-term single doses and long-term daily regimens (Rajaram et al., 2017; Zhang et al., 2023). Identifying the lowest effective doses or the highest toxicity levels is challenging without conducting dose-response studies. Age, health status, and genetic factors are among the elements that can influence the optimal dosage for various populations (Arias-Sánchez et al., 2023; Donno et al., 2020).

## **9.2 Limited clinical trials and human data**

There is a notable lack of research on nut bioactives in people who have existing cognitive impairments or diagnosed neurodegenerative diseases. The majority of the study groups included healthy adults or older individuals exhibiting normal cognitive function. To grasp how research findings can benefit a broader audience, it is essential to involve individuals from various races, age groups, and health statuses. Standardized cognitive assessments and biomarkers play a crucial role in supporting meta-analyses and allowing for the comparison of different studies. Reaching definitive conclusions about which cognitive domains might benefit from nut consumption is challenging, as various studies employed different cognitive assessments (Rajaram et al., 2017; Tan et al., 2022).

## **9.3 Bioavailability and Metabolism Challenges**

The bioavailability of the bioactive compounds in nuts is a big knowledge gap that makes it hard to move from preclinical to clinical efficacy. Many phenolic compounds are hard for the body to absorb because they don't dissolve well in water. Phase II metabolism, encompassing processes such as glucuronidation and sulfation, further reduces the concentration of active compounds within the tissues.

The bacteria residing in the gut decompose bioactive substances found in nuts, particularly phenolic compounds, into metabolites that the body can more readily utilize. Conversely, alterations in the gut microbiota can significantly influence the production of metabolites and the accessibility of these compounds to the body (Gorji et al., 2018).

To enhance the effectiveness of nut-based therapies, it is essential to understand the influence of the microbiome on these treatments. Neuroprotective compounds face significant challenges in crossing the blood-brain barrier, as many bioactive substances found in nuts show limited effectiveness in reaching the central nervous system. We need to learn more about the chemicals or metabolites that can easily get into brain tissue and keep it safe. It may be crucial to explore innovative methods for delivering drugs to the brain, such as nanoparticle formulations (Donno et al., 2020; Spadaro et al., 2020).

#### **9.4 Need for Multi-Targeted Approaches and Synergistic Formulation**

It is essential to develop plans that consider various factors and ensure that the components function harmoniously together. Given the complexity of cognitive impairment and the multitude of potential causes, treatments that rely solely on a single compound may not achieve their maximum effectiveness. It might be more beneficial to utilize therapies that concurrently tackle oxidative stress, neuroinflammation, protein aggregation, and synaptic dysfunction instead of concentrating on just one problem. Nut bioactive naturally affect different targets, but a lot of research needs to be done to find the best combinations.

Nut bioactive may collaborate to enhance overall activity, resulting in effects that surpass those of each individual component. We still do not completely grasp these synergistic connections, which indicates a need for more targeted research employing factorial designs and interaction analysis. One intriguing field of study centers on creating tailored formulations that maintain bioavailability while enhancing synergistic effects.

Nut bioactive may be more effective when combined with additional factors that support brain health, such as cognitive training, physical exercise, or other nutraceuticals. These lifestyle changes, when used together, may work better than just changing your diet because they give you real ways to keep your brain healthy.

#### **10. Conclusion**

This extensive study highlights the significant therapeutic potential of bioactive compounds found in nuts for maintaining cognitive health and offering neuroprotection. These compounds operate through various mechanisms across a range of disorders. Nuts, especially walnuts, are known for their wide range of bioactive compounds, including flavonoids, phenolic acids, tocopherols, and polyunsaturated fatty acids. These compounds work together to reduce the main harmful processes linked to cognitive decline. These substances safeguard the brain by functioning directly as antioxidants, regulating anti-inflammatory signaling, inhibiting cholinesterase, and enhancing pathways related to synaptic plasticity.

Comparative analyses of the phytochemical profiles and antioxidant capacities of major nut varieties reveal that pecans possess the highest levels of phenolic compounds and antioxidant capacity, walnuts are supported by the most clinical evidence for cognitive benefits, and almonds are richest in vitamin E content. Further investigation is necessary due to the intricate relationship between chemical composition and biological efficacy, which encompasses factors such as bioavailability, metabolism, and synergistic interactions.

Nut bioactive work together to influence oxidative stress, neuroinflammation, protein aggregation, and neurotransmitter systems via interconnected pathways, as demonstrated by the molecular insights provided. This multi-target strategy may offer benefits over therapies that focus on a single mechanism and corresponds with the complex, varied nature of cognitive impairment. Notably, potential therapeutic mechanisms include the bioactive properties of nuts, which bolster the body's natural antioxidant defenses, encourage anti-inflammatory signaling, and support neural plasticity.

To fully grasp the therapeutic potential of nut bioactive in cognitive health, numerous research gaps remain to be addressed, despite the encouraging evidence. The creation of consistent therapeutic interventions is hindered by the absence of standardized extraction methods, dosing guidelines, and quality assurance practices. The generalizability of the current findings is limited due to the lack of clinical trial data, especially regarding nuts other than walnuts and among populations with pre-existing cognitive impairment. There are some important things we don't know that could explain why preclinical promise and clinical outcomes are different. These include problems with bioavailability and a lack of understanding of metabolism and tissue distribution.

Future research should focus on developing standardized methods for extraction and formulation that enhance the concentration of bioactive compounds while ensuring consistency across batches. Extensive and prolonged clinical trials are essential to provide conclusive evidence of cognitive benefits across various demographics and medical conditions. Therapeutic effectiveness might be improved by investigating methods to enhance bioavailability, such as innovative delivery systems and synergistic formulations. Moreover, tailored strategies that take into account differences in metabolic capacity, gut microbiota composition, and genetic factors could enhance treatment outcomes.

The potential of nut bioactive to enhance cognitive health presents a fascinating convergence of nutritional research, neuroscience, and preventive medicine. Eating nuts and making other evidence-based dietary adjustments are promising, simple, and affordable methods to maintain brain health and potentially reduce the risk of neurodegenerative diseases as the

population ages and cognitive decline becomes increasingly prevalent. The extensive data collected in this study encourages further research and development of bioactive compounds derived from nuts as beneficial elements in holistic approaches aimed at improving cognitive health across the lifespan.

### 11. Acknowledgement

The authors would like to express their sincere gratitude to their mentors and colleagues for their invaluable guidance and support during the preparation of this review.

### 12. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this review.

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