Acta Scientific Neurology (ASNE)

Volume 9 Issue 7 July 2026

Review Article

From Lychee to Neurotherapeutics: Mechanistic, Gut–Brain, and Translational Perspectives on *Litchi chinensis* in Alzheimer's Disease

Karthik Chintharala[1]* and Amritaa Thalla[2]

[1]*NRI Academy of Medical Sciences, Guntur, India*

[2]*Maheshwara Medical College and Hospital, Telangana, India*

***Corresponding Author:** Karthik Chintharala, NRI Academy of Medical Sciences, Guntur, India.

Received: May 18, 2026

Published: July 07, 2026

DOI: 10.31080/ASNE.2026.09.0925

Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β deposition, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, chronic neuroinflammation, synaptic degeneration, and neuronal loss. Although currently available therapies, including acetylcholinesterase inhibitors such as donepezil, NMDA receptor antagonists such as memantine, and anti-amyloid monoclonal antibodies such as donanemab and lecanemab, provide symptomatic or modest disease-modifying benefits, their overall clinical impact remains limited. These limitations have increased interest in naturally derived compounds capable of targeting multiple neuropathological pathways implicated in Alzheimer's disease. Among these, *Litchi chinensis* has emerged as a rich source of bioactive phytochemicals with potential neuroprotective properties.

Review Focus: A comprehensive review of the available literature was conducted to evaluate the neuroprotective potential of *Litchi chinensis* and its phytoconstituents in Alzheimer's disease. Experimental studies investigating the effects of lychee-derived compounds on amyloid pathology, tau dysfunction, oxidative stress, neuroinflammation, apoptosis, synaptic impairment, and neuronal survival were critically synthesized.

Key Findings: Preclinical studies suggest that *Litchi chinensis*-derived compounds, including catechins, procyanidins, flavanols, saponins, and oligonol, exert neuroprotective effects through multiple complementary mechanisms. These phytochemicals have been reported to reduce amyloidogenic processing by modulating amyloid precursor protein and β-secretase activity, suppress tau hyperphosphorylation through regulation of the IRS-1/PI3K/Akt/GSK-3β signaling pathway, attenuate oxidative stress by enhancing endogenous antioxidant defences, and inhibit neuroinflammatory responses involving NF-κB and NLRP3 signaling. Additional reported effects include modulation of apoptotic pathways, preservation of synaptic proteins and blood–brain barrier integrity, enhancement of autophagy, and regulation of neurotrophic and metabolic signaling pathways associated with neuronal survival and cognitive function.

Future Perspectives: Current preclinical evidence suggests that *Litchi chinensis* and its bioactive constituents warrant further investigation as potential adjunctive therapeutic candidates for Alzheimer's disease. However, clinical translation remains limited, and additional studies are required to establish standardized formulations, characterize pharmacokinetic properties, evaluate long-term safety, and determine therapeutic efficacy in human populations.

Keywords: Alzheimer's Disease; *Litchi chinensis*; Lychee; Oligonol; Polyphenols; Amyloid-B; Tau; Neuroinflammation; Oxidative Stress; Neuroprotection

Abbreviations

Aβ: Amyloid-beta; AD: Alzheimer's Disease; Akt: Protein Kinase B; AMPK: AMP-Activated Protein Kinase; APP: Amyloid Precursor Protein; APP/PS1: Amyloid Precursor Protein/Presenilin-1 Transgenic Mouse Model; BACE1: Beta-site Amyloid Precursor Protein Cleaving Enzyme 1; Bax: Bcl-2-associated X protein; BBB: Blood–Brain Barrier; Bcl-2: B-Cell Lymphoma 2; BV-2: Murine Microglial Cell line BV-2; CAT: Catalase; ER: Endoplasmic Reticulum; FGF21: Fibroblast Growth Factor 21; GPx: Glutathione Peroxidase; Gpx1: Glutathione Peroxidase 1; GSK-3β: Glycogen Synthase Kinase-3 Beta; HO-1: Heme Oxygenase-1; IFN: Interferon; IFN-γ: Interferon-Gamma; IGF-2: Insulin-like Growth Factor 2; IL: Interleukin; IRS-1: Insulin Receptor Substrate-1; mTOR: Mammalian Target of Rapamycin; NF-κB: Nuclear Factor-Kappa B; NLRP3: NOD-like Receptor Family Pyrin Domain-containing 3; PI3K: Phosphoinositide 3-kinase; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSD95: Postsynaptic Density Protein 95; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; SOD: Superoxide dismutase; SOD2: Superoxide Dismutase 2; TIMP-1: Tissue Inhibitor of Metalloproteinases-1; TNF-α: Tumor Necrosis Factor-Alpha; ULK1: Unc-51-like kinase 1; ZO-1: Zonula Occludens-1.

Introduction

Alzheimer's disease is the leading cause of dementia, which accounts for approximately two-thirds of cases worldwide, imposing a steadily growing burden on patients, caregivers, and healthcare systems [1,2]. Clinically, the disorder manifests with progressive deficits in episodic memory, executive function, language, and behaviour, eventually resulting in profound functional dependence [3]. The global prevalence of dementia is projected to increase sharply over the coming decades as populations age, making the development of effective preventive and therapeutic strategies a major public health priority [4].

The neuropathological landscape of Alzheimer's disease is defined by extracellular accumulation of amyloid-β peptides and intracellular aggregation of hyperphosphorylated tau into neurofibrillary tangles, but these hallmark lesions represent only part of a broader network of pathogenic processes [5]. Soluble Aβ oligomers disrupt synaptic transmission, calcium homeostasis, and mitochondrial function, while abnormal phosphorylation of tau results in destabilization of microtubules and deficits in axonal transport [6]. Activated microglia and astrocytes secrete pro-inflammatory cytokines, which lead to increased neuronal damage and excessive reactive oxygen species, which induce oxidative damage to lipids, proteins, and nucleic acids [7]. These interconnected mechanisms result in synaptic failure, neuronal loss, and a progressive decline in cognition [8].

Despite decades of research, currently approved therapies remain only partially effective. Acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) and NMDA receptor antagonists such as memantine improve symptoms in select patients but do not alter disease progression [9]. Anti-amyloid monoclonal antibodies such as lecanemab and donanemab have introduced a new therapeutic paradigm for patients with only mild cognitive impairment, yet their benefits are modest, and their implementation is constrained by monitoring requirements, cost, and adverse effects, notably amyloid-related imaging abnormalities [10,11]. The multifactorial pathological nature of Alzheimer's disease suggests that effective intervention may require agents capable of modulating several pathogenic pathways simultaneously rather than targeting a single molecular event [12].

Natural products have emerged as an important source of compounds with pleiotropic biological activities relevant to neurodegeneration [13]. Polyphenols and related phytochemicals can exert antioxidant, anti-inflammatory, anti-apoptotic, and synaptoprotective effects while influencing intracellular signaling pathways linked to amyloid processing and tau phosphorylation [14]. This multitarget pharmacology has generated a considerable interest in plant-derived agents such as lychee as a potential adjunctive therapy for Alzheimer's disease.

Litchi chinensis Sonn., commonly known as lychee, is a subtropical fruit cultivated widely in China, India, and Southeast Asia and consumed globally as both a food and a traditional medicinal resource [15]. While the edible aril is valued for its nutritional content, the seed contains a concentrated array of procyanidins, catechins, and saponins with documented biological activity [16]. Oligonol, a low-molecular-weight polyphenol preparation derived from lychee, has attracted particular attention because of its improved bioavailability and broad antioxidant and anti-inflammatory properties [17]. Over the past decade, a growing body of preclinical work has demonstrated that lychee-derived compounds attenuate amyloid accumulation, suppress tau

pathology, modulate neuroinflammation, reduce oxidative stress, and improve cognition in experimental models of Alzheimer's disease [18,19].

Literature search strategy

A literature search for this narrative review was conducted through a comprehensive search of PubMed/MEDLINE, Web of Science, Scopus, Science Direct, and Google Scholar databases up to January 2026. A combination of keywords including "*Litchi chinensis*", "lychee", "Alzheimer's disease", "neuroinflammation", "oxidative stress", "amyloid-beta", "tau pathology", "gut-brain axis", "polyphenols", and "neuroprotection" was used. A preference was given to experimental, mechanistic, translational, and clinical studies relevant to neurodegeneration and Alzheimer's dementia. Additional references were identified through manual screening of reference lists from relevant articles.

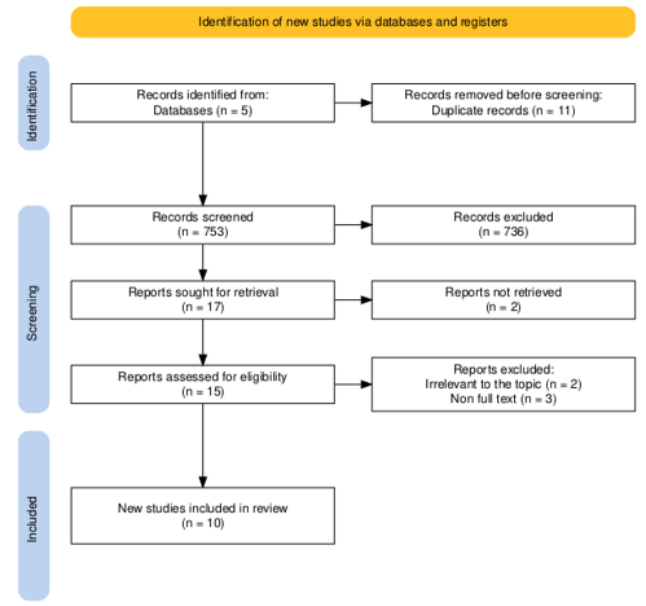

Figure 1: Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimized digital transparency and Open Synthesis Campbell System.

Phytochemical Profile and Pharmacological Significance of *Litchi chinensis*

Litchi chinensis is abundant in bioactive molecules present in the pulp, peel and seed. The seed is the most plentiful source of neuroactive phytochemicals [20]. The most well-studied constituents are catechin, epicatechin, procyanidin A1, procyanidin A2 and triterpenoid saponins, which have been associated with antioxidant and anti-inflammatory effects in experimental systems [21]. These molecules contain structural features that allow for direct scavenging of free radicals and for modulation of signaling pathways that are involved in inflammation, apoptosis, and metabolic regulation [22].

Oligonol, a proprietary compound obtained by depolymerization of proanthocyanidins isolated from lychee, is the most widely studied lychee bioproduct in neurodegenerative research [23]. Oligonol enhances intestinal absorption and systemic bioavailability of large polymeric polyphenols by breaking them down into low-molecular-weight oligomers and monomers, which is one of the most frequently encountered limitations of plant polyphenols [24]. In animal studies, oligonol showed good safety and tolerability and has been demonstrated to influence oxidative stress, inflammatory responses, mitochondrial metabolism, and neuronal survival pathways [18,19].

Beyond direct antioxidant activity, the pharmacological significance of *Litchi chinensis* is further augmented by the modulation of insulin signaling, inhibition of glycogen synthase kinase-3β, suppression of NF-κB activation and regulation of autophagic pathways through AMPK/mTOR/ULK1 signaling by compounds derived from lychee [25]. As these mechanisms overlap with major pathogenic processes in Alzheimer's disease, the phytochemical profile of *Litchi chinensis* provides a biologically plausible basis for its neuroprotective effects.

Mechanistic basis of neuroprotection in Alzheimer's disease

Modulation of amyloidogenic processing

Amyloid-β accumulation is widely regarded as an early event in Alzheimer's disease pathogenesis, particularly in familial and biomarker-defined forms of the disorder [26]. Experimental studies consistently show that lychee-derived compounds reduce APP expression, inhibit BACE1, and decrease cerebral Aβ burden [23,27]. In triple-transgenic mice, oligonol substantially lowered

APP and BACE1 levels and was associated with reduced plaque-related pathology and improved cognitive performance [18]. Similar reductions in Aβ were observed with lychee seed extracts and isolated polyphenols in both cellular and animal models [25].

Inhibition of Tau hyperphosphorylation

Tau's abnormal phosphorylation leads to destabilization of microtubules and is directly involved in neuronal dysfunction and the formation of neurofibrillary tangles [28]. Multiple studies demonstrated that *Litchi chinensis* inhibits GSK-3β, one of the main kinases involved in tau regulation, and attenuates tau pathology [29]. Lychee seed polyphenols activate the IRS-1/PI3K/Akt pathway which negatively regulates GSK-3β and reduces tau hyperphosphorylation [25]. Seed fractions and oligonol reduced phosphorylated tau levels and improved cognitive outcomes *in vivo* [18,29].

Inhibition of neuroinflammation

Chronic activation of glial cells results in neuronal damage through the release of TNF-α, IL-1β, IL-6, IFN-γ and other pro-inflammatory mediators [30]. Lychee seed polyphenols significantly reduce these cytokines in BV-2 microglial cells and transgenic mouse models [27]. Oligonol also increases IL-4, suggesting a shift towards a more anti-inflammatory environment [18]. Lychee seed polyphenol inhibits NLRP3 inflammasome activation in endothelial and animal models, further decreasing neuroinflammatory signaling [31].

Attenuation of oxidative stress and mitochondrial dysfunction

Alzheimer's disease pathology is both a result of and a driver of oxidative stress [32]. Oligonol decreases lipid peroxidation and nitric oxide production, and upregulates antioxidant enzymes such as glutathione peroxidase-1 and superoxide dismutase-2 [33]. These changes are associated with better expression of mitochondrial and metabolic genes, implying a more extensive role in restoring cellular bioenergetics [33].

Inhibition of apoptosis

Apoptotic neuronal death is a major cause of hippocampal and cortical atrophy in Alzheimer's disease [35]. Lychee seed saponins and polyphenols upregulate BCL-2, downregulate BAX, and inhibit caspase-3 activation in neuronal and microglial models [36]. These coordinated effects favor cell survival and reduce structural neuronal injury *in vivo* [21].

Preservation of synaptic integrity and cognitive function

Synaptic loss correlates more closely with cognitive decline than either amyloid plaque burden or tangle density [34]. Oligonol increases the expression of PSD95, synaptophysin and synapsin II proteins, which are essential for synaptic plasticity and neurotransmission [35]. These molecular changes are associated with improvement of spatial learning, recognition memory and behavioral performance in several experimental models [18,24].

Blood-brain barrier protection, autophagy, and neurotrophic signaling

Beyond canonical AD pathways, lychee-derived compounds protect endothelial integrity, enhance autophagic flux, and promote neurotrophic support [19,31]. The activation of the AMPK/mTOR/ULK1 signaling promotes the clearance of damaged proteins and organelles and the increase of IGF-2, FGF21 and TIMP-1 may have a role in neuronal survival and tissue remodelling [19,31]. These findings suggest that compounds obtained from *Litchi chinensis* may affect wider homeostasis mechanisms than neuroprotection per se, but this has to be confirmed.

Experimental Focus	Lychee- Derived Compound	Key Observations	Biological Pathways Involved	Translational Considerations
Amyloid modulation	Oligonol; seed polyphenols	Reduced APP, BACE1, and amyloid-β accumulation in cellular and transgenic models	Regulation of amyloidogenic processing pathways	Findings remain limited to preclinical systems
Tau pathology	Catechins, procyanidins, seed extracts	Attenuation of tau hyperphosphorylation and improved neuronal signaling	IRS-1/PI3K/Akt/GSK-3β modulation	Optimal dosing and BBB penetration remain uncertain
Neuroinflammation	Lychee seed fractions; oligonol	Suppression of TNF-α, IL-1β, IL-6, IFN-γ, and related inflammatory mediators	NF-κB and NLRP3 inflammasome regulation	Lack of clinical inflammatory biomarker studies
Oxidative stress	Oligonol	Reduced lipid peroxidation and enhancement of antioxidant enzyme activity	Upregulation of Gpx1, Sod2, and related antioxidant systems	Human pharmacokinetic evidence remains limited

Apoptosis regulation	Seed saponins and polyphenols	Increased BCL-2 expression with reduction of BAX and caspase activation	Mitochondrial apoptotic pathway modulation	Long-term safety data are insufficient
Synaptic preservation	Oligonol	Improved synaptic protein expression and behavioral performance	PSD95, synaptophysin, and synapsin-related pathways	Cognitive benefits not yet validated clinically
Blood–brain barrier protection	Lychee seed polyphenols	Improved endothelial integrity and autophagic activity	AMPK/mTOR/ULK1 signaling	Translational reproducibility requires further study
Neurotrophic and Metabolic support	Oligonol	Increased IGF-2, FGF21, and mitochondrial regulatory markers	Neurotropic and metabolic signaling pathways	Clinical significance Remains exploratory

Table 1: Representative Experimental Evidence Supporting the Neuroprotective Potential of Litchi chinensis in Alzheimer's Disease Models.

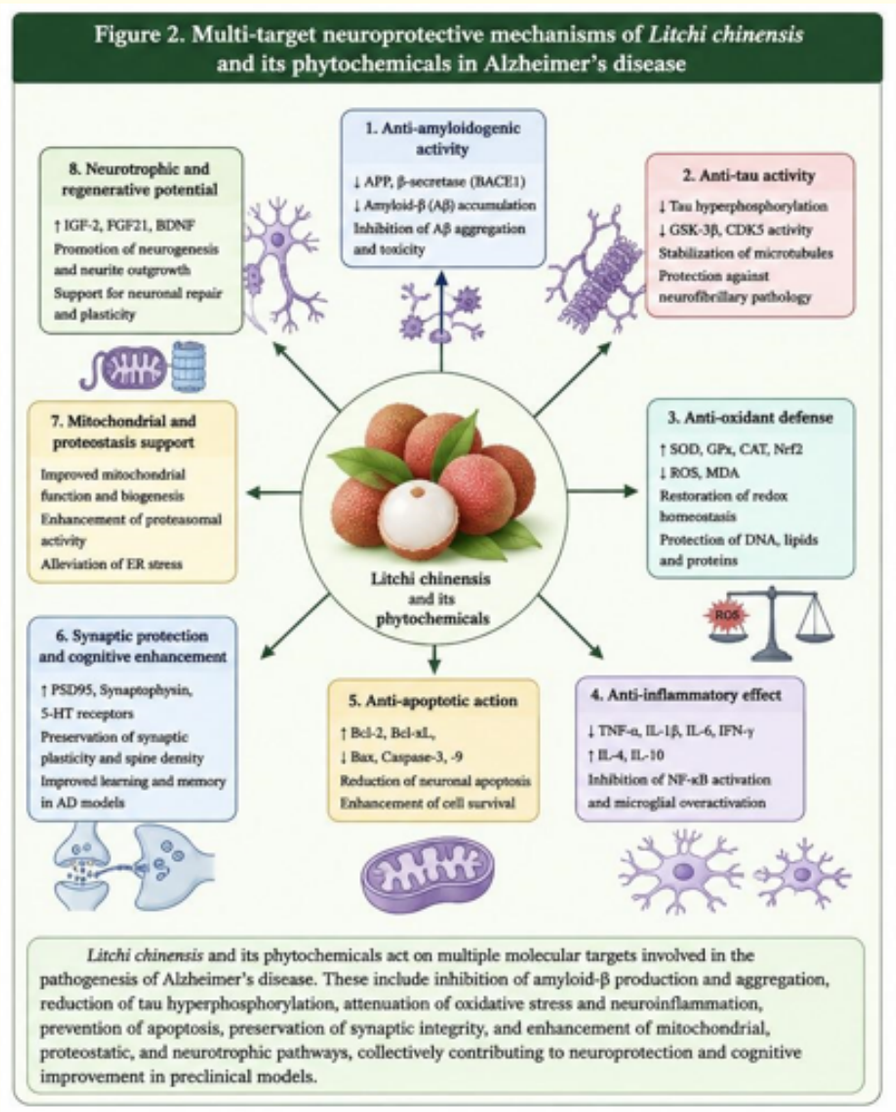

Figure 2: Integrated mechanistic model showing the effects of lychee-derived compounds on amyloid processing, tau phosphorylation, neuroinflammation, oxidative stress, apoptosis, synaptic plasticity, and blood-brain barrier integrity. IGF-2, Insulin-like growth factor-2, FGF21, fibroblast-like growth factor 21, BDNF, APP, BACE1, GSK-3B, CDK5, ER, endoplasmic reticulum, SOD, superoxide dismutase, GPx, CAT, Nrf2, ROS, reactive oxygen species, MDA, DNA, deoxyribonucleic acid, PSD95, HT, histamine, AD, Alzheimer's dementia, BCL-2, BCL-XL, BAX, TNF-a, IL-1b, IL-6, IFN-gamma, IL - interleukin , NK-KB.

Gut–brain axis as a possible mediator of neuroprotective effects of lichi chinensis

The modulation of gut microbial and neuroinflammatory pathways based on indirect mechanistic evidence is another mechanism proposed for the neuroprotective effects of *Litchi chinensis* phytochemicals. There is increasing evidence that dietary polyphenols are widely metabolized by intestinal microbiota to smaller phenolic metabolites with better bioavailability as well as various biological activities in peripheral tissues and the central nervous system. These metabolites can affect intestinal barrier integrity, decrease endotoxemia, modify short-chain fatty acid production, and suppress systemic inflammation [37,38].

This is especially true for lychee-derived compounds as catechins, epicatechins and procyanidins are well-established substrates for microbial metabolism. Their transformation by gut bacteria may yield bioactive metabolites capable of crossing the blood–brain barrier and modulating signaling pathways implicated in Alzheimer's disease [27]. The anti-inflammatory and antioxidant effects documented for *Litchi chinensis*, include reductions in TNF-α, IL-1β, and IL-6 and preservation of endothelial integrity [27]. This is consistent with mechanisms commonly attributed to microbiome-mediated neuroprotection [38]. At present, direct experimental or clinical evidence specifically evaluating *Litchi chinensis*-mediated modulation of the gut microbiome in Alzheimer's disease remains limited. Therefore, the proposed gut-brain interactions discussed in this review should primarily be interpreted as a hypothesis-generating perspective. This can supported by an indirect mechanistic evidence derived from related polyphenolic compounds and broader neuroinflammatory research.

Future studies integrating metagenomics, metabolomics, and microbiome profiling may help clarify whether *Litchi chinensis*-derived phytochemicals can meaningfully influence gut microbial composition, neuroimmune signaling, and neurodegenerative pathways relevant to Alzheimer's disease.

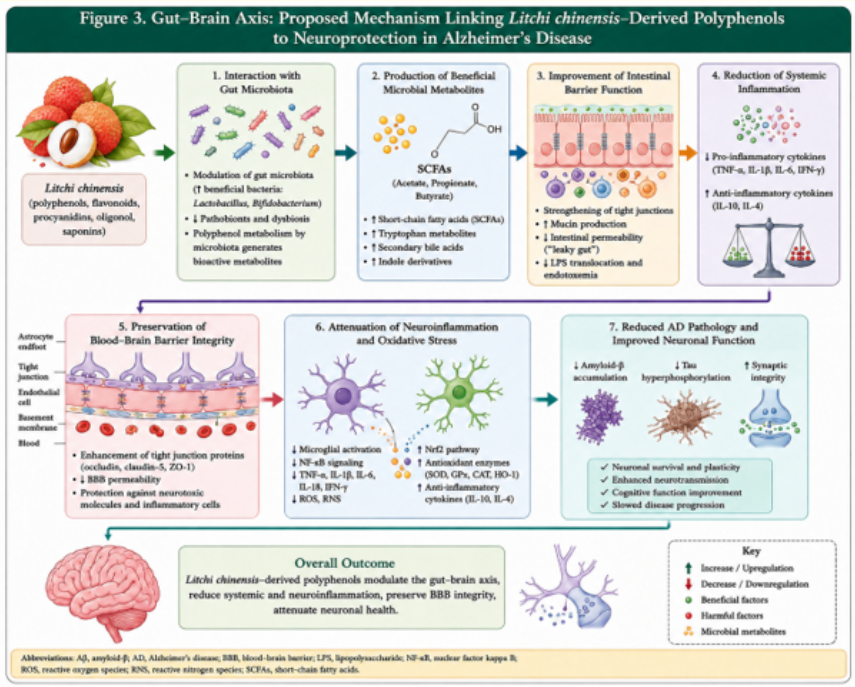

Figure 3: Gut–brain axis as a proposed mechanism linking Litchi chinensis-derived polyphenols to neuroprotection in Alzheimer's disease. Litchi chinensis phytochemicals may affect gut microbiota and increase beneficial microbial metabolites, gut and blood–brain barrier integrity, and systemic and neuroinflammation. These processes could potentially lower oxidative stress, sustain neuronal function and promote cognition. The suggested mechanisms are mostly supported by preclinical and mechanistic evidence and require further clinical validation.

Clinical evidence and translational relevance

Although the mechanistic and preclinical evidence supporting *Litchi chinensis* is compelling, direct clinical evidence in Alzheimer's disease remains unexplored. This gap is not unique to lychee-derived compounds and reflects a broader challenge in the translation of botanical neuroprotective agents. Many natural products with strong experimental data, including curcumin, resveratrol, and epigallocatechin gallate, have demonstrated favourable biological effects in animal models but only modest or inconsistent clinical benefits, often because of limited bioavailability, inadequate dosing strategies, and heterogeneity in patient populations [39]. The clinical development of lychee-derived polyphenols is nonetheless supported by several favourable characteristics. First, lychee has a long history of dietary consumption, suggesting an overall acceptable safety profile when used in standardized formulations. Second, oligonol was specifically engineered to improve oral absorption, which may provide an advantage over less bioavailable polyphenols. Third, the broad mechanistic effects of *Litchi chinensis* including anti-inflammatory, antioxidant, anti-amyloid, and anti-tau actions, which align well with the current concepts of Alzheimer's disease as a multifactorial disorder.

One potential future translational application could involve individuals with mild cognitive impairment or biomarker-confirmed early Alzheimer's disease, where neuronal loss is less advanced and disease-modifying interventions are more likely to demonstrate benefit. Early phase trials should focus on safety, pharmacokinetics, CSF and plasma biomarkers and exploratory cognitive endpoints. Biomarkers such as Amyloid-β 42/40 ratio, phosphorylated tau 217, isoform genetic testing, presence of neurofilament light chain and inflammatory cytokines would help to establish biological activity and inform dose selection.

Comparison with other neuroprotective polyphenols

Natural polyphenols have been extensively investigated for their neuroprotective properties, as they can modulate oxidative stress, neuroinflammation and protein aggregation. Curcumin has been reported to inhibit NF-κB signaling and reduce amyloid aggregation, but its clinical use is limited by poor absorption and rapid metabolism. Resveratrol has been shown to activate SIRT1 and improve mitochondrial function, but high doses are often necessary to achieve measurable systemic exposure. Epigallocatechin gallate has been shown to inhibit amyloid fibrillization and attenuate oxidative stress but its stability and bioavailability challenge [40].

Lychee polyphenols are in a special position in this wide spectrum of activities. Oligonol contains low-molecular-weight catechin and procyanidin derivatives designed for improved intestinal absorption. In addition to the well-documented antioxidant and anti-inflammatory effects, *Litchi chinensis* has demonstrated concurrent regulation of APP processing, GSK-3β-mediated tau phosphorylation, autophagy and endothelial protection. Such a broad range of activities suggests that lychee-derived formulations are reasonable candidates for further translational investigation.

Limitations of current evidence

Several limitations should be considered when interpreting the existing literature. The evidence base is composed almost entirely of *in vitro* and animal studies, and direct extrapolation to human disease must therefore be approached cautiously. Experimental models capture only selected aspects of Alzheimer's disease and do not fully reproduce the biological neuropathology and slow progression observed in human subjects.

There is also substantial methodological heterogeneity across studies. Different parts of the plant, extraction procedures, purification methods and dosing schedules have been used by investigators hampering comparison between studies. Some reports did not fully characterize the precise composition and concentration of active compounds. Sample sizes were often small and long-term toxicity, pharmacokinetics and drug-interaction data are still scant. Inconsistent standardization of bioactive compound quantification between studies restricts reproducibility and direct comparison of findings. Furthermore, blood–brain barrier penetration and dose optimization remain poorly characterized for many *Litchi chinensis*-derived compounds. Publication bias for positive preclinical findings may also exaggerate therapeutic potential.

Future research priorities

Future research should focus on understanding the molecular mechanisms of neuroprotective effects of *Litchi chinensis*-derived compounds through integrated multi-omic, pharmacokinetic and translational approaches with particular attention to standardization of phytochemical composition, blood-brain

barrier penetration, long-term safety evaluation and validation in clinically relevant *in vitro*, animal and then human models. In addition, further studies exploring gut-brain interactions and neuroimmune signaling may help better define the therapeutic relevance of *Litchi chinensis* in Alzheimer's disease research. At present, many proposed mechanisms remain exploratory and hypothesis-generating, pending further translational and clinical validation.

Translational perspective and future directions

The preclinical literature presents a coherent and biologically plausible picture in which *Litchi chinensis* acts through multiple complementary mechanisms relevant to Alzheimer's disease [19,24]. This breadth of activity is particularly attractive in a disorder driven by interacting pathological cascades rather than a single causative pathway [12]. Oligonol and related lychee-derived polyphenols also compare favorably with other natural compounds such as curcumin, resveratrol, and epigallocatechin gallate, especially because oligonol was specifically developed to improve oral bioavailability [41].

Nevertheless, substantial barriers remain before clinical application can be considered. Most studies involve small animal cohorts or cell-based models, and there is considerable heterogeneity in extraction methods, compound characterization, dosing regimens, and outcome measures [29]. Data regarding blood-brain barrier penetration, metabolite profiles, and pharmacokinetic behaviour in humans are sparse. Long-term safety appears favourable in experimental models, but comprehensive toxicology and drug-interaction studies are still needed [39].

Future research should prioritize standardized formulations, mechanistic biomarker studies, and carefully designed phase I and phase II clinical trials in individuals with mild cognitive impairment or early Alzheimer's disease. Translation of molecular benefits observed in experimental models into meaningful clinical effects will require an integration of neuroimaging, fluid biomarkers, and pharmacodynamic endpoints.

Conclusion

Litchi chinensis represents an emerging source of multifunctional bioactive compounds with potential neuroprotective relevance in Alzheimer's disease research. Across a growing body of experimental studies, lychee-derived polyphenols and saponins appear to reduce amyloid burden in invitro/animal studies, suppress tau hyperphosphorylation, attenuate oxidative stress and neuroinflammation, prevent apoptosis, preserve synaptic integrity, and improve cognition [18,19,29,31]. The convergence of these effects across diverse models supports the concept that *Litchi chinensis* may function as a potential multi-adjunctive target neuroprotective strategy requiring further validation.

Although the translational pathway remains incomplete, the existing evidence provides a reasonable basis for further investigation. With advances in formulation science, biomarker-guided clinical trials, and rigorous standardization of active constituents, lychee-derived compounds may ultimately contribute to preventive or adjunctive therapeutic strategies aimed at slowing the progression of Alzheimer's disease.

Bibliography

1. Mayeux R and Stern Y. "Epidemiology of Alzheimer disease". C*old Spring Harbor Perspectives in Medicine* 2.8 (2012): a006239.

2. World Health Organization. "Global status report on the public health response to dementia". WHO (2021).

3. Sohrabi HR and Weinborn M. "Cognitive Impairments in Alzheimer's Disease and Other Neurodegenerative Diseases". In Neurodegeneration and Alzheimer's Disease (eds R. N. Martins, C.S. Brennan, W.M.A.D.B. Fernando, M.A. Brennan and S.J. Fuller) (2019).

4. Guerchet M., *et al*. "Numbers of people with dementia worldwide: an update to the estimates in the World Alzheimer Report". *Alzheimer's Disease International* (2017).

5. Harris GA., *et al*. "Revisiting the therapeutic landscape of tauopathies: assessing the current pipeline and clinical trials". *Alzheimer's Research Therapy* 17.1 (2025): 129.

6. de Felice FG., *et al*. "Aβ oligomers induce neuronal oxidative stress and synaptic dysfunction". *Journal of Biological Chemistry* 279 (2004): 33139-33145.

7. Wang X., *et al*. "Oxidative stress and mitochondrial dysfunction in Alzheimer's disease". *Biochimica et Biophysica Acta* 1842.8 (2014): 1240-1247.

8. Tönnies E and Trushina E. "Oxidative stress, synaptic dysfunction, and mitochondrial failure in Alzheimer's disease". *Journal of Alzheimer's Disease* 57 (2017): 1105-1121.

9. Hansen RA., *et al*. "Efficacy and safety of donepezil, galantamine, and rivastigmine for Alzheimer's disease". *Clinical Interventions in Aging* 3 (2008): 211-225.

10. Wrigley S., *et al*. "Monoclonal Antibody Therapies in Alzheimer's Disease: A Guide for Emergency Physicians". *Emergency Medicine Australasia* 37.6 (2025): e70167.

11. Yashooa RK., *et al*. "CRISPR-Cas technologies in neurodegenerative disorders: mechanistic insights, therapeutic potential, and translational challenges". *Frontiers in Neurology* 16 (2026): 1737468.

12. Iqubal A., *et al*. "Current Quest in Natural Bioactive Compounds for Alzheimer's Disease: Multi-Targeted-Designed-Ligand Based Approach with Preclinical and Clinical Based Evidence". *Current Drug Targets* 22 (2021): 685-720.

13. Chen B., *et al*. "Neuroprotective effects of natural compounds on neurotoxin-induced oxidative stress and cell apoptosis". *Nutritional Neuroscience* 25.5 (2022): 1078-1099.

14. Shoaib S., *et al*. "Plant-Derived Bioactive Compounds in the Management of Neurodegenerative Disorders: Challenges, Future Directions and Molecular Mechanisms Involved in Neuroprotection". *Pharmaceutics* 15.3 (2023): 749.

15. A Mohamed., *et al*. "Litchi chinensis: Medicinal uses, phytochemistry, and pharmacology". *Journal of Ethnopharmacology* 174 (2015).

16. Kanwal Rabia., *et al*. (2024). Litchi.

17. Choi YY., *et al*. "Oligonol improves memory and cognition under an amyloid β (25-35)-induced Alzheimer's mouse model". *Nutrition Research* 34.7 (2014): 595-603.

18. Desai MK., *et al*. "Triple-transgenic Alzheimer's disease mice exhibit region-specific abnormalities in brain myelination patterns prior to appearance of amyloid and tau pathology". *Glia* 57.1 (2009): 54-65.

19. Jo Y., *et al*. "Oligonol enhances mitochondrial and synaptic function in aged and Alzheimer's disease models". *Ageing Research Review* (2023).

20. Ibrahim SR and Mohamed GA. "Litchi chinensis: medicinal uses, phytochemistry, and pharmacology". *Journal of Ethnopharmacology* 174 (2015): 492-513.

21. Wang X., *et al*. "Inhibitory Effect of Lychee Seed Saponins on Apoptosis Induced by Aβ25-35 through Regulation of the Apoptotic and NF-κB Pathways in PC12 Cells". *Nutrients* 9.4 (2017): 337.

22. Habtemariam S. "Natural Products in Alzheimer's Disease Therapy: Would Old Therapeutic Approaches Fix the Broken Promise of Modern Medicines?" *Molecules* 24.8 (2019): 1519.

23. Lee AY., *et al*. "Preventive effect of oligonol on nitric oxide and reactive oxygen species production through regulation of nuclear factor kappa B signaling pathway in RAW 264.7 macrophage cells against sodium nitroprusside". *RSC Advances* 9.7 (2019): 3987-3993.

24. Choi SY., *et al*. "Oligonol enhances brain cognitive function in high-fat diet-fed mice". *Biomed Pharmacotherapy* 179 (2024): 117322.

25. Xiong R., *et al*. "Polyphenols isolated from lychee seed inhibit Alzheimer's disease-associated Tau through improving insulin resistance via the IRS-1/PI3K/Akt/GSK-3β pathway". *Journal of Ethnopharmacology* 251 (2020): 112548.

26. Haass C and Selkoe DJ. "Cellular processing of beta-amyloid precursor protein and the genesis of amyloid beta-peptide". *Cell* 75.6 (1993): 1039-1042.

27. Tang Y., *et al*. "Polyphenols Derived from Lychee Seed Suppress Aβ (1-42)-Induced Neuroinflammation". *International Journal of Molecular Sciences* 19.7 (2018): 2109.

28. Barbier P., *et al*. "Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects". *Frontiers in Aging Neuroscience* 11 (2019): 204.

29. Long HZ., *et al*. "PI3K/AKT Signal Pathway: A Target of Natural Products in the Prevention and Treatment of Alzheimer's Disease and Parkinson's Disease". *Frontiers in Pharmacology* 12 (2021): 648636.

30. Heneka MT., *et al*. "Neuroinflammation in Alzheimer's disease". *Lancet Neurology* 14.4 (2015): 388-405.

31. Xiong R., *et al*. "Lychee seed polyphenol protects the blood-brain barrier through inhibiting Aβ (25-35)-induced NLRP3 inflammasome activation via the AMPK/mTOR/ULK1-mediated autophagy in bEnd.3 cells and APP/PS1 mice". *Phytotherapy Research* 35.2 (2021): 954-973.

32. Tönnies E and Trushina E. "Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease". *Journal of Alzheimer's Disease* 57.4 (2017): 1105-1121.

33. Jo D., *et al*. "Oligonol ameliorates liver function and brain function in the 5 × FAD mouse model: transcriptional and cellular analysis". *Food Function* 14.21 (2023): 9650-9670.

34. Tu S., *et al*. "Oligomeric Aβ-induced synaptic dysfunction in Alzheimer's disease". *Molecular Neurodegeneration* 9 (2014): 48.

35. Budson Andrew E. author.; Solomon, Paul R., author. Edinburgh: Elsevier; 2016 Library Catalog; MMS ID 9916673333406676; ISBN 9780323286619; NLM Unique ID 101667333.

36. Qiu WQ., *et al*. "Lychee seed polyphenol inhibits Aβ-induced activation of NLRP3 inflammasome via the LRP1/AMPK mediated autophagy induction". *Biomed Pharmacotherapy* 130 (2020): 110575.

37. Cryan JF., *et al*. "The gut microbiome in neurological disorders". *Lancet Neurology* 19.2 (2020): 179-194.

38. Chintharala K., *et al*. "The Gut Microbiome And Its Impact On Neurological Health: A Systematic Review". *Journal of Neurological Sciences and Research* 4.1 (2024).

39. Cummings J., *et al*. "Alzheimer's disease drug development pipeline: 2021". *Alzheimer's Dement (N Y)* 7.1 (2021): e12179.

40. Ringman JM., *et al*. "A potential role of the curry spice curcumin in Alzheimer's disease". *Current Alzheimer Research* 2.2 (2005): 131-136.

41. Thirunavukkarasu M., *et al*. "Safety of oligonol, a highly bioavailable lychee-derived polyphenolic antioxidant, on liver, kidney and heart function in rats". *Toxicology Mechanisms and Methods* 22.7 (2012): 555-559.