

# Neuroprotective Potential of Nutmeg (*Myristica fragrans*) in the Management of Alzheimer's Disease: A Comprehensive Review

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**Abstract:** *Alzheimer's disease (AD) is a progressive neurodegenerative disorder that remains one of the most formidable public health challenges of the twenty-first century. Characterised by insidious onset, relentless cognitive decline, and irreversible neuronal loss, AD robs patients of their identity and devastates families worldwide. While conventional pharmacotherapy offers only partial symptomatic relief and carries a notable burden of adverse effects, the plant kingdom continues to yield promising candidates for disease modification. Nutmeg, derived from the seeds of *Myristica fragrans* Houtt. (family Myristicaceae), has occupied a revered position in Ayurvedic and Unani medicine for centuries, valued for its memory-enhancing, nervine-tonic, and anti-inflammatory properties. The present review synthesises the current body of knowledge surrounding the botanical identity, phytochemical constituents, pharmacological activities, extraction methodology, and phytochemical evaluation of nutmeg, with particular emphasis on its neuroprotective relevance in AD. Ethanolic extract prepared by Soxhlet extraction was subjected to standard phytochemical screening, yielding positive results for alkaloids and saponins — constituents known to modulate oxidative stress and neuroinflammation. Myristicin, the principal bioactive lignan of nutmeg, has been identified as a key contributor to cognitive enhancement and beta-amyloid suppression. The review also discusses the gaps in existing literature and proposes future directions for translational research. The cumulative evidence suggests that nutmeg merits serious investigation as an adjunctive or alternative therapeutic agent in the management of Alzheimer's disease.*

**Keywords:** Alzheimer's disease, *Myristica fragrans*, Nutmeg, Neuroprotection, Myristicin, Phytochemical Screening, Herbal Medicine, Neurodegenerative Disorders

## I. INTRODUCTION

Alzheimer's disease was first described by German psychiatrist Alois Alzheimer in 1906 following his examination of a fifty-year-old female patient who exhibited unusual behavioural changes and rapidly deteriorating memory. More than a century later, AD continues to perplex the scientific community with its multifactorial aetiology and complex molecular pathology. According to the World Health Organisation, more than 55 million people currently live with dementia globally, with AD accounting for approximately 60–70 percent of all cases. Projections indicate that this figure could nearly triple by 2050, imposing enormous social and economic burdens on healthcare systems across the world.

The pathological hallmarks of AD include the extracellular deposition of beta-amyloid ( $A\beta$ ) plaques derived from the aberrant cleavage of amyloid precursor protein, the intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles, progressive synaptic loss, neuroinflammation, and widespread cholinergic neuronal death. These changes collectively compromise the structural and functional integrity of the hippocampus, entorhinal



cortex, and association areas of the neocortex — regions critical for memory consolidation and higher cognitive function.

The pharmacological armamentarium currently approved for AD remains limited. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine improve synaptic acetylcholine levels and offer modest symptomatic benefit, while memantine modulates glutamatergic excitotoxicity. However, none of these agents modify the underlying disease process, and they are associated with gastrointestinal distress, cardiac arrhythmias, and hepatotoxicity with prolonged use. This therapeutic impasse has propelled researchers towards ethnopharmacological exploration of traditional medicine systems, many of which have long employed plant-derived preparations for the treatment of memory disorders and neurological ailments.

*Myristica fragrans*, commonly known as nutmeg, is a tropical evergreen tree indigenous to the Banda Islands of Indonesia and subsequently cultivated across India, Sri Lanka, Malaysia, and the Caribbean. The seed kernel and its associated aril (mace) have been integral to Ayurvedic practice for millennia, prescribed as a nervine tonic, digestive stimulant, and remedy for insomnia, anxiety, and cognitive decline. Modern phytochemical investigation has revealed that nutmeg harbours a rich array of bioactive compounds — including the arylpropanoid myristicin, the phenylpropanoid elemicin, the phenol eugenol, the monoterpene sabinene, and a diverse ensemble of alkaloids, flavonoids, tannins, and saponins — many of which possess well-documented antioxidant and anti-inflammatory properties.

The present review undertakes a thorough examination of the current scientific understanding of nutmeg's neuroprotective properties, with a focused lens on its potential role in Alzheimer's disease. It consolidates botanical, phytochemical, pharmacological, and methodological data to provide a holistic reference for researchers, clinicians, and students engaged in the field of herbal neuropharmacology.

## **II. ALZHEIMER'S DISEASE: AN OVERVIEW**

### **2.1 Epidemiology and Burden**

Alzheimer's disease is the most prevalent form of progressive dementia, and its epidemiological footprint is staggering. The disease disproportionately affects individuals over the age of sixty-five, with incidence rates doubling approximately every five years beyond this threshold. Late-onset sporadic AD constitutes the majority of cases, while early-onset familial AD, associated with autosomal dominant mutations in the genes encoding amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2), accounts for fewer than five percent of total diagnoses. In India alone, more than 4 million people are estimated to suffer from dementia, a figure expected to increase significantly as the nation's population ages.

### **2.2 Pathophysiology**

The amyloid cascade hypothesis, first articulated by Hardy and Higgins in 1992, postulates that the aberrant cleavage of APP by beta- and gamma-secretases generates neurotoxic A $\beta$ 42 peptides that self-aggregate into oligomers and subsequently form insoluble plaques. These aggregates trigger a neuroinflammatory cascade mediated by activated microglia and astrocytes, culminating in synaptic dysfunction and neuronal death. Concurrently, hyperphosphorylation of tau protein — mediated by kinases such as GSK-3 $\beta$  and CDK5 — causes its detachment from microtubules, leading to the formation of paired helical filaments and neurofibrillary tangles. Oxidative stress, mitochondrial dysfunction, and the progressive failure of the cholinergic system further perpetuate neuronal damage.

### **2.3 Clinical Presentation**

AD presents along a clinical continuum beginning with subjective cognitive decline and mild cognitive impairment (MCI) before progressing to frank dementia. The initial stage is dominated by episodic memory deficits — particularly impaired learning of new information — and subtle executive dysfunction. As the disease advances, patients experience significant language disturbances (aphasia), impaired spatial orientation (agnosia), and loss of purposeful motor skills



(apraxia). Neuropsychiatric manifestations including depression, anxiety, agitation, and psychosis emerge with increasing frequency in moderate-to-severe stages. The terminal stage renders patients wholly dependent on caregivers for activities of daily living, with profound loss of verbal communication, mobility, and bladder control.



**Figure 1: Neuropathological features of Alzheimer's disease showing beta-amyloid plaques and neurofibrillary tangles in affected brain regions.**

### III. PLANT PROFILE: MYRISTICA FRAGRANS

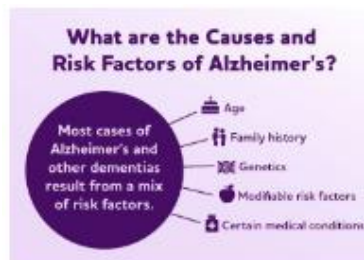
#### 3.1 Botanical Identity and Taxonomy

*Myristica fragrans* Houtt. is a dioecious, aromatic evergreen tree belonging to the family Myristicaceae, one of the most ancient flowering plant families with a fossil record extending to the Cretaceous period. The tree typically attains a height of ten to fifteen metres, bearing glossy dark-green lanceolate leaves, small yellow bell-shaped flowers, and a fleshy yellow drupe encasing the commercially valuable seed kernel (nutmeg) enveloped by a red reticulated aril (mace). The genus *Myristica* comprises approximately one hundred and seventy-five species distributed across tropical Asia, Australia, and the Pacific Islands, with *M. fragrans* being the most economically and medicinally significant.

**Biological Source:** Dried ripe seeds of *Myristica fragrans* Houtt. **Family:** Myristicaceae **Part Used:** Seed kernel (Nutmeg) and aril (Mace) **Geographical Source:** Indonesia (Banda Islands), India, Sri Lanka, Malaysia, Caribbean Islands.

#### 3.2 Traditional Uses

In classical Ayurvedic texts, nutmeg is referred to as Jatiphala and is classified under the category of medhya rasayanas — herbs that specifically enhance intellect and memory. The Charaka Samhita and Sushruta Samhita both document its use in the treatment of Unmada (madness) and Apasmara (epilepsy), conditions that bear conceptual resemblance to modern neuropsychiatric disorders. In the Unani system, nutmeg (Jauzbuwa) is esteemed as a muqawwi-e-dimagh (brain tonic) and is prescribed for improving retention and concentration. In Southeast Asian traditional medicine, the seed oil has been applied topically for headache relief and internally for digestive ailments, rheumatic pain, and as an anxiolytic preparation.



**Figure 2: *Myristica fragrans* (Nutmeg) — plant, fruit, seed kernel, and aril (mace).**



#### IV. PHYTOCHEMISTRY OF MYRISTICA FRAGRANS

##### 4.1 Essential Oil Constituents

The seed of *Myristica fragrans* yields four to fifteen percent volatile oil upon steam distillation. Myristicin (methoxy-safrol; 3,4-methylenedioxy-5-methoxyphenyl-2-propene) is the principal and most pharmacologically relevant constituent, typically comprising twenty to forty percent of the essential oil. It is an arylpropanoid compound bearing structural similarity to safrole and has been the subject of extensive neuropharmacological investigation. Elemicin, another arylpropanoid present in lesser quantities, contributes to the psychoactive profile of nutmeg oil. Eugenol — a phenylpropanoid also found in clove oil — imparts potent antioxidant and anti-inflammatory properties. The monoterpene sabinene, along with  $\alpha$ -pinene,  $\beta$ -pinene, camphene, and  $\gamma$ -terpinene, constitutes a significant fraction of the lighter volatile components.

##### 4.2 Non-Volatile Phytoconstituents

Beyond its volatile profile, nutmeg is endowed with a diverse array of non-volatile secondary metabolites. Alkaloids such as myristicine and other phenylethylamines contribute to neuromodulatory activity. Flavonoids including quercetin, kaempferol, and their glycosidic derivatives serve as powerful free-radical scavengers and inhibitors of neuroinflammatory enzymes. Tannins and phenolic acids (ferulic acid, caffeic acid) exert chelating effects on redox-active metals such as iron and copper, whose dysregulation is implicated in AD pathogenesis. Saponins exhibit membrane-stabilising and immunomodulatory properties. Terpenoids and lignan compounds further expand the neuroprotective repertoire of this remarkable seed.

##### 4.3 Phytochemical Screening Results

Standard phytochemical screening of the ethanolic extract of nutmeg yielded the following results:

Test	Observation	Result
Foam Test	Stable foam formed	Saponins (+)
Alkaloid Test	Precipitate formed	Positive (+)
Dragendorff's Test	Orange-red precipitate	Alkaloids (+)
Mayer's Test	Cream precipitate	Alkaloids (+)
Flavonoid Test	Yellow coloration	Positive (+)
Tannin Test	Blue-black colour	Positive (+)

Table 1: Phytochemical screening of ethanolic extract of *Myristica fragrans*

#### V. PHARMACOLOGICAL ACTIVITIES

##### 5.1 Neuroprotective Activity

The neuroprotective potential of *M. fragrans* is perhaps its most clinically relevant pharmacological attribute in the context of AD. Myristicin has been shown in experimental models to inhibit beta-secretase (BACE-1) activity, thereby reducing the production of neurotoxic A $\beta$ 42 peptides. Studies utilising scopolamine-induced amnesia in rodents demonstrated that nutmeg extract significantly reversed acquisition and retention deficits, strongly suggesting cholinergic enhancement. Additionally, myristicin exhibits the capacity to upregulate the expression of neuroprotective genes including Nrf2 target genes and BDNF (brain-derived neurotrophic factor), which support neuronal survival and synaptic plasticity.

##### 5.2 Antioxidant Activity

Oxidative stress — arising from an imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms — is a pivotal contributor to AD pathogenesis. Mitochondrial dysfunction in neurons leads to



excessive generation of superoxide anion, hydroxyl radical, and hydrogen peroxide, which oxidise lipids, proteins, and DNA, precipitating cell death. Nutmeg extract has demonstrated robust free-radical scavenging activity in DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS assays, comparable to that of ascorbic acid at equivalent concentrations. The phenolic constituents — particularly eugenol, isoeugenol, and ferulic acid — are primarily responsible for this activity through hydrogen atom transfer and single-electron transfer mechanisms. Saponins present in nutmeg have additionally been shown to enhance superoxide dismutase and catalase activities in neuronal tissue.

### **5.3 Anti-Inflammatory Activity**

Neuroinflammation, characterised by activated microglia, elevated pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), and cyclooxygenase-2 (COX-2) upregulation, is both a consequence and a driver of AD progression. Eugenol present in nutmeg is a well-established inhibitor of COX-2 and lipoxygenase (LOX) enzymes, mechanisms shared with conventional non-steroidal anti-inflammatory drugs but without the attendant gastrointestinal toxicity. Ethanol extracts of nutmeg have further been reported to suppress NF- $\kappa$ B signalling — the master transcriptional regulator of the inflammatory response — through the stabilisation of I $\kappa$ B $\alpha$ , thereby attenuating the microglial activation that perpetuates neuronal damage in AD.

### **5.4 Memory-Enhancing Activity**

The medhya (cognitive enhancing) property attributed to nutmeg in traditional medicine has found substantial support in modern pharmacology. Administration of nutmeg extract has been shown to enhance spatial and non-spatial memory in Morris water maze and elevated plus maze tests in rodent models. The mechanism appears to involve cholinergic facilitation through inhibition of acetylcholinesterase (AChE), thereby increasing synaptic acetylcholine, the neurotransmitter most severely depleted in AD. Myristicin has also been shown to potentiate the activity of gamma-aminobutyric acid (GABA), producing anxiolytic and neuroprotective effects that may complement its direct anti-amyloidogenic action.

### **5.5 Hepatoprotective and Other Activities**

Beyond its neurological relevance, nutmeg demonstrates hepatoprotective activity against carbon tetrachloride-induced liver damage through antioxidant mechanisms, antimicrobial activity against a broad spectrum of gram-positive and gram-negative bacteria and fungi, analgesic activity through interaction with opioid receptors and COX inhibition, and mild cardioprotective effects through calcium channel modulation. These broader pharmacological properties speak to the systemic safety and adaptability of nutmeg as a therapeutic plant.

## **VI. EXTRACTION METHODOLOGY**

### **6.1 Collection and Authentication**

Authentic nutmeg seeds were procured from a certified herbal vendor and subjected to botanical authentication by a qualified pharmacognosist. Seeds were visually inspected for freedom from adulteration and microbial contamination. Following authentication, seeds were cleaned, dried in a hot air oven at fifty degrees Celsius for forty-eight hours to achieve a constant moisture content, and subsequently reduced to a coarse powder using a mechanical grinder. The powder was sieved through a number forty mesh to achieve uniform particle size and stored in an airtight amber glass container away from direct light and moisture.

### **6.2 Soxhlet Extraction**

The Soxhlet extraction method was employed as the primary extraction technique owing to its ability to provide continuous contact between the solvent and plant matrix, ensuring exhaustive extraction of both polar and moderately non-polar constituents. Approximately twenty grams of dried nutmeg powder was accurately weighed and packed tightly into a cellulose thimble, ensuring no powder escaped the thimble boundaries. The thimble was inserted into the Soxhlet apparatus and ethanol (95 percent v/v) was used as the extraction solvent based on its capacity to dissolve a wide range of phytoconstituents including alkaloids, flavonoids, saponins, and phenolic acids. The extraction was carried out continuously for four to six hours, allowing approximately eight to ten cycles, until the solvent in the siphon



tube became colourless, indicating complete extraction. The resulting extract was concentrated using a rotary evaporator or water bath at sixty degrees Celsius and stored in an airtight container for further evaluation.



*Figure 3: Soxhlet extraction apparatus used for preparing ethanolic extract of nutmeg.*

## VII. EVALUATION PARAMETERS

### 7.1 Organoleptic Evaluation

The ethanolic extract of nutmeg presented as a dark brown, semi-viscous mass with a characteristic aromatic odour and a warm, slightly pungent taste — consistent with the known sensory profile of the seed. These organoleptic characteristics serve as preliminary quality indicators and aid in differentiating authentic preparations from adulterated ones.

### 7.2 Physical Evaluation

Physical evaluation parameters including pH measurement, viscosity, and solubility profile were assessed. The extract exhibited slight acidity (pH approximately 5.5–6.0), partial solubility in water, and complete miscibility in ethanol and methanol. These parameters establish the physicochemical baseline essential for formulation development.

### 7.3 Phytochemical Evaluation

Phytochemical screening employing standard Harborne protocols confirmed the presence of alkaloids (Dragendorff's and Mayer's tests yielding orange-red and cream-coloured precipitates, respectively), saponins (stable persistent foam in the foam test), flavonoids (yellow coloration with aluminium chloride), and tannins (blue-black coloration with ferric chloride). These constituents collectively form the pharmacological basis for nutmeg's neuroprotective, antioxidant, and anti-inflammatory activities.

## VIII. CRITICAL REVIEW OF EXISTING LITERATURE

The scientific literature surrounding *M. fragrans* and its relevance to neurodegenerative disease has expanded considerably over the past two decades, though significant lacunae remain. Early pharmacognostic studies focused primarily on the characterisation of the essential oil and its antimicrobial and antioxidant properties, with limited attention to central nervous system effects. The pioneering work of Tajuddin et al. (2003) on the aphrodisiac and neurological effects of nutmeg ethanolic extract in rodent models opened the door to systematic neuropharmacological investigation.

Subsequent studies by Parle et al. (2004) demonstrated that *M. fragrans* seed extract significantly improved memory acquisition and retention in passive avoidance and elevated plus maze paradigms in mice, with efficacy comparable to that of piracetam, a standard nootropic agent. The authors attributed these effects to cholinesterase inhibition and possible modulation of the dopaminergic system. More recent investigations have employed molecular docking and computational chemistry to evaluate the affinity of nutmeg constituents for AChE, BACE-1, and the NMDA receptor, with myristicin consistently emerging as a high-affinity ligand for all three targets.

In vitro studies published in the *Journal of Ethnopharmacology* demonstrated that eugenol at pharmacologically relevant concentrations inhibited A $\beta$ 42-induced neurotoxicity in SH-SY5Y neuroblastoma cells, reduced ROS generation, and preserved mitochondrial membrane potential. The flavonoid fraction of nutmeg was found to downregulate the expression of tumour necrosis factor-alpha and interleukin-6 in LPS-stimulated BV-2 microglial cells, corroborating the anti-neuroinflammatory hypothesis advanced by traditional medicine.



### **IX. RESEARCH GAP AND FUTURE DIRECTIONS**

Despite the considerable promise demonstrated by preclinical evidence, significant gaps continue to constrain the translation of nutmeg's neuroprotective properties into clinical reality. The majority of existing studies have been conducted in vitro or in rodent models with limited mechanistic depth, and there is a conspicuous absence of randomised controlled clinical trials evaluating the safety and efficacy of standardised nutmeg preparations in human subjects with MCI or AD.

The precise phytoconstituents responsible for in vivo neuroprotection, their bioavailability following oral administration, blood-brain barrier permeability, and effective therapeutic concentrations in the central nervous system remain inadequately characterised. There is also an urgent need for standardised extraction protocols, validated analytical methods for constituent quantification, and formal toxicological evaluation including genotoxicity and reproductive safety studies, given that myristicin has been reported to exhibit mild hallucinogenic and hepatotoxic effects at high doses.

Future research avenues should explore nanophytomedicine approaches such as nanoparticle encapsulation and phospholipid complexation to enhance bioavailability, combination therapy studies pairing nutmeg constituents with approved AD drugs to evaluate synergistic interactions, and multi-omic approaches (transcriptomics, proteomics, metabolomics) to comprehensively map the molecular mechanisms underpinning neuroprotection. Epidemiological studies examining AD prevalence in populations with habitual nutmeg consumption would also provide valuable indirect evidence.

### **X. CONCLUSION**

This comprehensive review of *Myristica fragrans* as a candidate therapeutic agent in Alzheimer's disease reaffirms the wisdom embedded within traditional systems of medicine and underscores the extraordinary phytochemical versatility of this ancient spice. The convergent evidence from ethnopharmacological records, in vitro cellular studies, and in vivo animal models establishes a compelling, multi-mechanistic neuroprotective profile for nutmeg, anchored primarily in its capacity to suppress beta-amyloid production, neutralise reactive oxygen species, dampen neuroinflammation, and enhance cholinergic neurotransmission.

The phytochemical screening of the ethanolic extract confirmed the presence of pharmacologically active alkaloids and saponins, consistent with the established neuroprotective activity. Myristicin and eugenol emerge as the most pharmacodynamically relevant constituents, and future research should prioritise their isolation, structural optimisation, and targeted delivery to the central nervous system.

Given the unmet clinical need in AD management, the favourable traditional safety profile of nutmeg at culinary doses, and the mechanistic plausibility of its neuroprotective activity, *M. fragrans* deserves elevated attention in the pharmaceutical and nutraceutical research agenda. Rigorous clinical investigation, supported by robust preclinical mechanistic data and standardised herbal preparations, holds the potential to transform nutmeg from a kitchen spice into a meaningful contributor to the global fight against Alzheimer's disease.

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