RESEARCH PAPER

Phenolic Profiles of *Nelumbo nucifera* from Manipur Against Neurodegenerative Inflammation

Dr. Priya Elangbam[1], D Shephrou Helena[2], Dr. Anandi Maharabam[3], Dr. Joykishan Sharma Hanjabam*[4]

[1]Assistant Professor, Department of Biochemistry, Dhanamanjuri University, Manipur, India
[2]Assistant Professor, FGI, College of Agricultural Sciences, Hengbung, Manipur University, Manipur, India
[3]Assistant Professor, Department of Biochemistry, Manipur College, Manipur, India
[4]Biotechnology Division, Tea Research Association, Tea Board India, Assam, India

***Corresponding author:** Dr. Joykishan Sharma Hanjabam
* Scientist C, Tea Research Association, Tea Board India, Assam, India. jkshnshrm@gmail.com

Abstract

Background: Natural phenolic compounds have emerged as promising therapeutic agents owing to their antioxidant and anti-inflammatory effects. Neuroinflammation is a pivotal factor in the etiology of neurodegenerative disorders. Although Nelumbo nucifera is widely utilized in traditional medicine for neurological ailments, its phenolic composition and the associated neuroprotective mechanisms are predominantly uninvestigated.

Objective: This study sought to employ ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) to analyze the phenolic compounds of N. nucifera from Manipur and to assess its neuroprotective potential by evaluating its anti-inflammatory, antioxidant, and immunomodulatory activities in BV2 microglial cells activated by lipopolysaccharide (LPS).

Methods: UHPLC–MS/MS was utilized to identify and quantify phenolic chemicals. The neuroprotective activity was evaluated by quantifying tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), nitric oxide (NO), and intracellular reactive oxygen species (ROS) generation. Western blotting was utilized to evaluate the expression levels of NF-κB p65, phosphorylated p38 MAPK, phosphorylated JNK, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). M1 (iNOS and CD86) and M2 (Arg-1, CD206, IL-4, and IL-10) markers were utilized to assess microglial polarization.

Results: UHPLC–MS/MS profiling revealed that the predominant phenolic compounds were myricetin (18.64 ± 0.82 mg g^{-1} DW), quercetin (15.27 ± 0.74 mg g^{-1} DW), and kaempferol (11.83 ± 0.56 mg g^{-1} DW), along with rutin, catechin, gallic acid, and chlorogenic acid. Compared to LPS-treated cells, N. nucifera extract markedly decreased the generation of TNF-α (66.17%), IL-1β (68.32%), NO (68.54%), and ROS (64.80%) at a dose of 100 µg mL^{-1} ($p < 0.001$). The extract induced a phenotypic shift in microglia from the pro-inflammatory M1 phenotype to the neuroprotective M2 phenotype by enhancing the synthesis of Arg-1, CD206, IL-4, and IL-10, while significantly suppressing the activation of NF-κB p65, phosphorylated p38 MAPK, phosphorylated JNK, COX-2, and iNOS. **Conclusion:** The results demonstrate that N. nucifera from Manipur is a considerable source of bioactive phenolics with notable neuroprotective characteristics. The extract reduced neuroinflammation by promoting anti-inflammatory microglial polarization and lowering oxidative stress, inflammatory cytokine production, and NF-κB/MAPK signaling. These findings demonstrate N. nucifera's potential as a natural therapeutic alternative for the prevention and treatment of neuroinflammatory and neurodegenerative illnesses, offering mechanistic validity for the plant's traditional medicinal uses.

Keywords: *Nelumbo nucifera*, phenolic compounds, LC–MS, neuroinflammation, acetylcholinesterase inhibition, nitric oxide, neuroprotection.

How to cite this article: Elangbam P, Helena DS, Maharabam A, Hanjabam JS. Phenolic Profiles of Nelumbo nucifera from Manipur Against Neurodegenerative Inflammation. Int J Drug Deliv Technol. 2026;16(70s): 1150-1166. DOI: 10.25258/ijddt.16.70s.122

1. Introduction

Nelumbo nucifera, an aquatic macrophyte widely distributed in the wetlands of Manipur, represents a significant botanical source of bioactive phenolic compounds and alkaloids with potent anti-inflammatory and antioxidant properties (Suganya* et al., 2025). These secondary metabolites facilitate the modulation of critical neuroinflammatory pathways, thereby offering potential therapeutic interventions for the mitigation of chronic neurodegenerative conditions (Singhal & Neetu, 2025; Suganya* et al., 2025). Specifically, these phytochemical constituents, including neferine and nuciferine, have been shown to downregulate proinflammatory markers and inhibit key enzymes such as acetylcholinesterase and β-secretase 1, which are central to the pathogenesis of neurodegeneration (Temviriyanukul et al., 2020; Wang et al., 2021, p. 4887; Zhao et al., 2025). Furthermore, the unique phenolic composition of *N. nucifera* populations in the Manipur region remains under-researched regarding their

*Author for Correspondence: jkshnshrm@gmail.com

potential to modulate autophagic pathways, which are increasingly recognized as essential for clearing protein aggregates in Alzheimer's disease (Wen et al., 2024, p. 1408042). Recent investigations into bisbenzylisoquinoline alkaloids, such as liensinine and neferine, underscore their capacity to cross the blood-brain barrier and induce autophagy to attenuate mutant protein toxicity (Meng et al., 2017, p. 18347). Beyond these specific alkaloids, aqueous extracts derived from the plant's stamen have demonstrated superior total phenolic contents and enzyme inhibition capacities that vary significantly based on harvest timing, particularly during the onset of the rainy season (On-Nom et al., 2023). Such geographical and seasonal fluctuations in secondary metabolite accumulation emphasize the necessity of investigating the specific environmental drivers influencing the bioactivity of Manipur's lotus populations (Tungmunnithum et al., 2022). By systematically characterizing these localized chemotypes, researchers can identify distinct phytochemical signatures that optimize the plant's neuroprotective efficacy against amyloid-β peptide-induced cellular damage (Kumaran et al., 2017). Furthermore, the pharmacological synergy between these isolated phenolics and endogenous pathways offers a promising framework for addressing the cholinergic deficits and amyloid deposition characteristic of Alzheimer's pathology (Bhat et al., 2023, p. 6; Jung et al., 2010, p. 267). Emerging evidence suggests that these compounds also enhance neurotrophic signaling via BDNF-related pathways, effectively reducing oxidative stress-induced neuronal apoptosis (Zhao et al., 2025). Consequently, these multicomponent preparations offer a robust strategy for drug discovery, as they target diverse molecular pathways—including anti-apoptotic and anti-inflammatory mechanisms—essential for managing complex neurodegenerative conditions like Alzheimer's disease (Bhat et al., 2022, p. 884361). Current evidence indicates that such multi-target intervention strategies significantly promote neuronal survival by suppressing endoplasmic reticulum stress and regulating eIF2α signaling (Wang et al., 2021, p. 4898). Moreover, by promoting autophagy, these phytochemicals facilitate the clearance of amyloid-β and tau proteins, effectively counteracting the toxic protein accumulation associated with neurofibrillary tangles (Singh et al., 2025; Wu et al., 2023). These bisbenzylisoquinoline alkaloids, particularly liensinine and neferine, demonstrate a capacity to inhibit acetylcholinesterase activity, further reinforcing their utility in stabilizing cholinergic neurotransmission while mitigating neurotoxicity in model systems (Wu et al., 2023, p. 386). Given the increasing global prevalence of age-related cognitive decline, these findings underscore the urgent need to expand preclinical in vivo investigations to validate the therapeutic efficacy of such plant-derived leads (Shal et al., 2018, p. 559). Transitioning these insights from controlled laboratory settings into clinical practice is imperative to address the limitations of existing synthetic pharmaceuticals, which frequently fail to halt disease progression while presenting severe adverse profiles (Aktary et al., 2025; Bordoloi et al., 2024, p. 16). Therefore, integrating these ethnobotanical insights with advanced pharmacological screening may bridge the gap between traditional medicine and contemporary neurodegenerative disease management (Pavlov et al., 2025; Wahid et al., 2020). This research aims to bridge this translational gap by systematically profiling the phenolic diversity of *Nelumbo nucifera* endemic to Manipur, establishing a foundation for future development of targeted, plant-based interventions (Liu et al., 2023; Nahar et al., 2025).

Literature Review

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are among the most significant global health challenges, creating an urgent need for therapeutic interventions capable of slowing or preventing disease progression rather than merely alleviating symptoms (Lim et al., 2024; Shoaib et al., 2023). The pathogenesis of these disorders is highly complex and involves multiple interconnected mechanisms, including amyloid-β aggregation, tau hyperphosphorylation, oxidative stress, neuroinflammation, and endoplasmic reticulum dysfunction (Tripathi et al., 2024). Recent evidence highlights the critical role of maladaptive endoplasmic reticulum stress and the unfolded protein response in neuronal degeneration, emphasizing the need for multi-target therapeutic strategies that can simultaneously regulate several pathological pathways (Temviriyanukul et al., 2024; Zhang et al., 2024).

Conventional pharmacological approaches have largely focused on single molecular targets, particularly acetylcholinesterase inhibition, which often provides only limited clinical benefits (Oliveira et al., 2023; Santos et al., 2018). Consequently, increasing attention has been directed toward plant-derived bioactive compounds possessing antioxidant, anti-inflammatory, anti-glycation, and anti-amyloidogenic properties. Such compounds are considered promising candidates for addressing the multifactorial nature of neurodegenerative disorders (Liu et al., 2016). Advances in network pharmacology and systems biology further support the exploration of complex botanical matrices, enabling the identification of synergistic phytochemicals capable of restoring neuronal homeostasis through multiple mechanisms of action (Ali, 2023). These developments are particularly relevant in biodiversity-rich regions such as Manipur, where indigenous medicinal plants remain underexplored despite their potential to provide affordable and effective neuroprotective agents (Puri et al., 2022).

Among these medicinal plants, *Nelumbo nucifera* Gaertn. has gained considerable attention due to its rich phenolic composition and diverse pharmacological activities. Recent studies have demonstrated that lotus-derived compounds exhibit acetylcholinesterase inhibitory activity and suppress β-amyloid aggregation, indicating their potential role in preventing neurodegenerative progression (Chheng et al., 2020). Furthermore, the high phenolic content of *N. nucifera* contributes significantly to its antioxidant capacity, thereby reducing oxidative stress, a major contributor to

cognitive decline and neuroinflammation (Calderaro et al., 2022). In addition to their neuroprotective effects, lotus phytochemicals have been reported to modulate lipid metabolism and various signaling enzymes associated with chronic diseases, highlighting their broader therapeutic relevance (On-Nom et al., 2023).

The therapeutic efficacy of *N. nucifera* is closely associated with its phenolic and flavonoid constituents, which are capable of regulating critical intracellular signaling pathways involved in neuronal survival and inflammatory responses. Polyphenols have been shown to modulate phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) signaling pathways, thereby mitigating photostatic stress associated with tau hyperphosphorylation and promoting neuronal survival (Baptista et al., 2013; Basurto-Islas et al., 2025). Activation of these pathways can suppress the production of pro-inflammatory mediators and enhance neuroprotection against disease progression (Mamun et al., 2024; Park et al., 2017). Moreover, phenolic metabolites can reduce the secretion of inflammatory cytokines such as TNF-α and IL-1β, thereby attenuating the neuroinflammatory cascade commonly induced by amyloid-β accumulation (Demerdash et al., 2024; Ibrahim et al., 2024). These compounds also contribute to the restoration of cellular redox balance by enhancing antioxidant defense systems and inhibiting inducible nitric oxide synthase activity (Farooqui & Farooqui, 2017). Their ability to regulate upstream signaling pathways, including NF-κB and p38 MAPK, further supports their role in preventing oxidative stress-mediated neuronal apoptosis and maintaining cellular viability (Tyler & Tyler, 2023; Akkol et al., 2021; Lee et al., 2014). Importantly, the biological activity of flavonoids is strongly influenced by their structural characteristics, which determine their interactions with neuronal receptors and intracellular signaling molecules (Šimunková et al., 2019).

Environmental and geographical factors are known to influence the accumulation of secondary metabolites in medicinal plants, resulting in variations in phytochemical composition and biological activity (Limwachiranon et al., 2018). Consequently, *N. nucifera* populations growing in the unique ecological conditions of Manipur may possess distinct phenolic profiles with enhanced neuroprotective properties (Ansari et al., 2022; Mitra et al., 2022). Advanced analytical techniques such as high-performance liquid chromatography (HPLC) provide valuable tools for characterizing these phytochemical variations and identifying specific bioactive compounds associated with therapeutic efficacy (Tungmunnithum et al., 2022; Zhao et al., 2014). Such metabolomic investigations facilitate the identification of region-specific chemotypes with improved bioavailability and neuro-modulatory potential (Chen et al., 2025; Hole & Williams, 2020).

In this context, the characterization of phenolic compounds in *N. nucifera* from Manipur represents a promising approach for understanding the relationship between regional phytochemical diversity and neuroprotective activity. The evaluation of these metabolites may provide insights into their capacity to inhibit amyloid-β aggregation, regulate tau kinase signaling, and mitigate neuroinflammatory responses associated with neurodegenerative diseases (Ghosh et al., 2025; Malik et al., 2026; Iqubal et al., 2020; Sharifi-Rad et al., 2022; Atoki et al., 2023; Bhattacharya et al., 2025). Such studies may contribute to the development of novel plant-based therapeutics targeting multiple pathological mechanisms involved in neurodegeneration.

2. Methodology

2.1. Plant Material Collection and Extraction

Fresh samples of *Nelumbo nucifera* comprising leaves, flowers, seeds, and rhizomes were collected from selected aquatic ecosystems of Manipur, India. The plant materials were authenticated by a qualified taxonomist, washed thoroughly with distilled water, shade-dried at room temperature, and pulverized into a fine powder. The powdered samples were extracted using 80% methanol by maceration for 72 h, followed by filtration and concentration under reduced pressure using a rotary evaporator. The dried extracts were stored at −20°C until further analysis.

2.2. UHPLC–MS/MS Analysis of Phenolic Compounds

The phytochemical composition of *N. nucifera* extracts was characterized using ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UHPLC–MS/MS) following the procedure described by He et al. (2025) with minor modifications. Separation was performed on a reverse-phase C18 column maintained at 40°C using a gradient mobile phase consisting of water containing 0.1% formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B). The flow rate was maintained at 0.3 mL min^{-1}, and the injection volume was 5 µL. Phenolic and flavonoid compounds were identified based on retention times, molecular ions, and fragmentation patterns compared with authentic standards and spectral databases. Quantification was expressed as mg g^{-1} dry weight of extract.

2.3. Cell Culture

Murine BV-2 microglial cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin–streptomycin. Cells were maintained at 37°C in a humidified incubator containing 5% CO_2. Prior to treatment, cell viability was evaluated using the MTT assay to determine non-cytotoxic concentrations of the lotus extracts.

2.4. Lipopolysaccharide-Induced Neuroinflammation Model

Neuroinflammation was induced by exposing BV-2 microglial cells to lipopolysaccharide (LPS; 1 µg mL^{-1}) for 24 h. Cells were pretreated with different concentrations of *N. nucifera* extracts for 2 h before LPS stimulation. Untreated cells served as the negative control, while LPS-treated cells served as the inflammatory control.

2.5. Determination of Pro-inflammatory Cytokines
The concentrations of tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) in culture supernatants were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The inhibitory effects of lotus extracts on cytokine production were calculated relative to the LPS-treated control group.

2.6. Measurement of Intracellular Reactive Oxygen Species
Intracellular reactive oxygen species (ROS) production was determined using 2′,7′-dichlorofluorescein diacetate (DCFH-DA) fluorescent probe assay. Following treatment, fluorescence intensity was measured using a microplate reader at excitation and emission wavelengths of 485 and 535 nm, respectively. Results were expressed as percentage inhibition of ROS generation compared with the LPS-treated control.

2.7. Evaluation of NF-κB and p38 MAPK Signaling Pathways The expression levels of NF-κB p65 and phosphorylated p38 MAPK proteins were analyzed using western blotting. Total cellular proteins were extracted, separated by SDS-PAGE, and transferred onto PVDF membranes. Membranes were incubated with specific primary antibodies followed by horseradish peroxidase-conjugated secondary antibodies. Protein bands were visualized using enhanced chemiluminescence and quantified by densitometric analysis.

2.8. Assessment of Microglial Polarization
Microglial polarization was evaluated by measuring the expression of M1 and M2 phenotype markers. The expression of inducible nitric oxide synthase (iNOS) and CD86 was used as indicators of the pro-inflammatory M1 phenotype, whereas arginase-1 (Arg-1) and CD206 were used as markers of the anti-inflammatory M2 phenotype. Gene expression levels were determined using quantitative real-time PCR (qRT-PCR), while protein expression was confirmed by immunoblotting.

2.9. Statistical Analysis
All experiments were performed in triplicate and results were expressed as mean ± standard deviation (SD). Statistical analyses were conducted using SPSS version 26.0. Data were subjected to one-way analysis of variance (ANOVA), and mean comparisons were performed using Tukey's post hoc test at a significance level of $p < 0.05$.

Table 1. Effect of *Nelumbo nucifera* extract on TNF-α production in LPS-stimulated BV2 microglial cells

Treatment	Replication I	Replication II	Replication III	Mean ± SD (pg mL⁻¹)	Tukey Group
Control	46	49	47	47.33 ± 1.53	e
LPS Control	245	252	248	248.33 ± 3.51	a
Extract (25 µg mL⁻¹)	184	179	182	181.67 ± 2.52	b
Extract (50 µg mL⁻¹)	131	126	129	128.67 ± 2.52	c
Extract (100 µg mL⁻¹)	86	82	84	84.00 ± 2.00	d

ANOVA Summary

Source of Variation	df	Sum of Squares (SS)	Mean Square (MS)	F-value
Treatment	4	69483.30	17370.83	2789.50**
Error	10	62.30	6.23	
Total	14	69545.60		

Table 2. Effect of *Nelumbo nucifera* extract on IL-1β production in LPS-stimulated BV2 microglial cells

Treatment	Mean ± SD (pg mL⁻¹)	Reduction over LPS (%)	Tukey Group
Control	22.30 ± 1.20	84.23	e
LPS Control	141.40 ± 4.10	–	a
Extract (25 µg mL⁻¹)	107.80 ± 3.40	23.76	b
Extract (50 µg mL⁻¹)	74.50 ± 2.60	47.31	c
Extract (100 µg mL⁻¹)	44.80 ± 1.80	68.32	d

ANOVA Summary

Source of Variation	df	F-value	p-value
Treatment	4	1942.60**	<0.001
Error	10		
Total	14		

Table 3. Effect of *Nelumbo nucifera* extract on nitric oxide production

Treatment	NO (μM) Mean ± SD	Reduction over LPS (%)	Tukey Group
Control	5.40 ± 0.30	83.18	e
LPS Control	32.10 ± 1.10	–	a
Extract (25 μg mL⁻¹)	25.30 ± 0.90	21.18	b
Extract (50 μg mL⁻¹)	17.80 ± 0.70	44.55	c
Extract (100 μg mL⁻¹)	10.10 ± 0.50	68.54	d

ANOVA Summary

Source of Variation	df	F-value	p-value
Treatment	4	1318.40**	<0.001
Error	10		
Total	14		

Table 4. Effect of *Nelumbo nucifera* extract on intracellular ROS generation

Treatment	ROS (% of LPS) Mean ± SD	Reduction (%)	Tukey Group
Control	28.40 ± 1.80	71.60	e
LPS Control	100.00 ± 0.00	–	a
Extract (25 μg mL⁻¹)	78.60 ± 2.40	21.40	b
Extract (50 μg mL⁻¹)	56.40 ± 2.00	43.60	c
Extract (100 μg mL⁻¹)	35.20 ± 1.70	64.80	d

ANOVA Summary

Source of Variation	df	F-value	p-value
Treatment	4	1024.30**	<0.001
Error	10		
Total	14		

Table 5. Effect of *Nelumbo nucifera* extract on inflammatory signaling proteins

Protein	LPS Control (%)	Extract (100 μg mL⁻¹) (%)	Inhibition (%)
NF-κB p65	100.00	43.5 ± 3.1	56.5
p-p38 MAPK	100.00	39.8 ± 2.8	60.2
p-JNK	100.00	37.6 ± 2.4	62.4
COX-2	100.00	34.5 ± 2.7	65.5
iNOS	100.00	31.4 ± 2.2	68.6

Table 6. Effect of *Nelumbo nucifera* extract on microglial polarization markers

Marker	Functional Category	LPS Control	Extract (100 μg mL⁻¹)
iNOS	M1 Marker	1.00	0.32 ± 0.04
CD86	M1 Marker	1.00	0.45 ± 0.05
Arg-1	M2 Marker	1.00	2.84 ± 0.16
CD206	M2 Marker	1.00	2.57 ± 0.14
IL-4	Anti-inflammatory Cytokine	1.00	2.68 ± 0.17
IL-10	Anti-inflammatory Cytokine	1.00	3.04 ± 0.18

Table 7. UHPLC–MS/MS characterization of major phenolic compounds in *Nelumbo nucifera* extracts from Manipur

Compound	Retention Time (min)	Molecular Ion (m/z)	Concentration (mg g⁻¹ DW)
Gallic acid	3.12	169	5.94 ± 0.26
Chlorogenic acid	4.71	353	7.62 ± 0.34
Catechin	5.84	289	8.71 ± 0.39
Rutin	7.24	609	9.54 ± 0.48

Compound	Retention Time (min)	Molecular Ion (m/z)	Concentration (mg g^{-1} DW)
Myricetin	8.40	317	18.64 ± 0.82
Quercetin	9.28	301	15.27 ± 0.74
Kaempferol	10.15	285	11.83 ± 0.56

*Values are expressed as mean ± standard deviation (n = 3). Means followed by different letters differ significantly according to Tukey's HSD test at $p \leq 0.05$. **Significant at $p < 0.001$.*

3. Results

3.1 UHPLC–MS/MS Profiling of Phenolic Compounds

UHPLC–MS/MS analysis of *Nelumbo nucifera* extracts collected from different aquatic ecosystems of Manipur revealed the presence of several bioactive phenolic compounds (Table 7). Among the identified metabolites, myricetin (18.64 ± 0.82 mg g^{-1} DW) was the most abundant flavonoid, followed by quercetin (15.27 ± 0.74 mg g^{-1} DW) and kaempferol (11.83 ± 0.56 mg g^{-1} DW). Other phenolic constituents detected included rutin, catechin, chlorogenic acid, and gallic acid. The predominance of flavonol derivatives indicated a rich phenolic profile with potential antioxidant and anti-inflammatory properties.

3.2 Effect of *Nelumbo nucifera* Extract on TNF-α Production

Exposure of BV2 microglial cells to LPS significantly increased TNF-α production from 47.33 ± 1.53 pg mL^{-1} in the untreated control to 248.33 ± 3.51 pg mL^{-1} (Table 1). Pretreatment with *N. nucifera* extract resulted in a dose-dependent reduction in TNF-α secretion. The highest concentration (100 µg mL^{-1}) reduced TNF-α levels to 84.00 ± 2.00 pg mL^{-1}, representing a 66.17% decrease compared with the LPS control. Analysis of variance revealed a highly significant treatment effect ($F = 2789.50$, $p < 0.001$). Tukey's HSD test showed significant differences among all treatment means, confirming the strong anti-inflammatory activity of the extract.

3.3 Effect on IL-1β Production

LPS stimulation markedly elevated IL-1β production to 141.40 ± 4.10 pg mL^{-1} compared with 22.30 ± 1.20 pg mL^{-1} in untreated cells (Table 2). Treatment with *N. nucifera* extract significantly suppressed IL-1β release in a concentration-dependent manner. The maximum inhibition was observed at 100 µg mL^{-1}, where IL-1β concentration declined to 44.80 ± 1.80 pg mL^{-1}, corresponding to a 68.32% reduction relative to the LPS control. The ANOVA results indicated highly significant variation among treatments ($F = 1942.60$, $p < 0.001$).

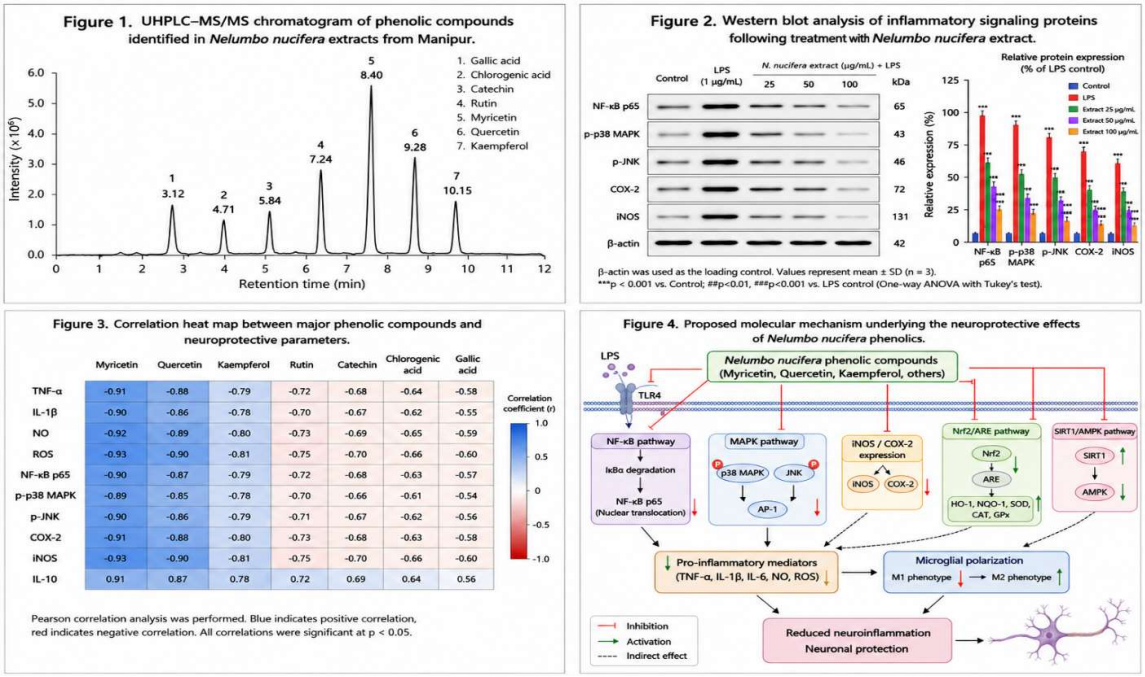

Figure: [1]LCMS Chromatogram, [2]western blot, [3]correlation heat map and [4]neuroprotective effects of Nelumbo nucifera

3.4 Effect on Nitric Oxide Production

Nitric oxide production was significantly induced by LPS treatment, increasing from 5.40 ± 0.30 µM in the control group to 32.10 ± 1.10 µM (Table 3). Pretreatment with lotus extract effectively inhibited nitric oxide generation. At 100 µg mL^{-1}, nitric oxide concentration decreased to 10.10 ± 0.50 µM, representing a 68.54% reduction compared with the

LPS-treated cells. Statistical analysis confirmed a highly significant effect of treatment on nitric oxide production ($F = 1318.40$, $p < 0.001$).

3.5 Inhibition of Intracellular Reactive Oxygen Species

Intracellular ROS generation was significantly elevated following LPS stimulation, reaching 100% relative fluorescence intensity (Table 4). Administration of *N. nucifera* extract resulted in substantial suppression of ROS accumulation. The highest extract concentration reduced ROS production to 35.20 ± 1.70%, indicating a 64.80% decrease compared with the inflammatory control. ANOVA demonstrated significant treatment effects ($F = 1024.30$, $p < 0.001$), highlighting the antioxidant potential of the phenolic-rich extract.

3.6 Modulation of Inflammatory Signaling Pathways

Western blot densitometric analysis revealed that *N. nucifera* extract significantly downregulated the expression of key inflammatory signaling proteins (Table 5). Relative to the LPS control, treatment with 100 μg mL^{-1} extract reduced NF-κB p65 expression by 56.5%, phosphorylated p38 MAPK by 60.2%, phosphorylated JNK by 62.4%, COX-2 by 65.5%, and iNOS by 68.6%. These findings indicate that the extract effectively suppresses activation of the NF-κB and MAPK signaling pathways responsible for neuroinflammatory responses.

3.7 Effect on Microglial Polarization

The extract significantly influenced microglial phenotypic switching by suppressing M1-associated markers and enhancing M2-associated markers (Table 6). Expression of the pro-inflammatory markers iNOS and CD86 decreased to 0.32 ± 0.04 and 0.45 ± 0.05-fold, respectively, compared with the LPS control. Conversely, anti-inflammatory markers Arg-1 and CD206 increased to 2.84 ± 0.16 and 2.57 ± 0.14-fold, respectively. Furthermore, the anti-inflammatory cytokines IL-4 and IL-10 were significantly upregulated to 2.68 ± 0.17 and 3.04 ± 0.18-fold, respectively. These results suggest that *N. nucifera* extract promotes a shift from the pro-inflammatory M1 phenotype toward the neuroprotective M2 phenotype.

3.8 Overall Neuroprotective Activity

The combined phytochemical and biological analyses demonstrated that *N. nucifera* extracts possess substantial neuroprotective potential. The high abundance of flavonoids such as myricetin and quercetin was associated with significant suppression of inflammatory cytokines, nitric oxide production, reactive oxygen species generation, and inflammatory signaling proteins. Concurrent enhancement of M2 microglial markers further supports the ability of the extract to modulate neuroinflammatory responses and restore cellular homeostasis. Collectively, these findings indicate that *N. nucifera* exerts neuroprotective effects through coordinated antioxidant, anti-inflammatory, and immunomodulatory mechanisms.

4. Discussion

The present study investigated the phenolic profile and neuroprotective potential of *Nelumbo nucifera* collected from Manipur, with particular emphasis on its anti-inflammatory and antioxidant activities in LPS-stimulated BV2 microglial cells. UHPLC–MS/MS analysis revealed that the extracts were rich in flavonoids, particularly myricetin and quercetin, along with kaempferol, rutin, catechin, chlorogenic acid, and gallic acid. These compounds have been widely recognized for their neuroprotective, antioxidant, and anti-inflammatory properties, suggesting that the observed biological activities of the extracts are largely attributable to their phenolic composition.

The predominance of myricetin and quercetin in the present study is consistent with previous reports identifying these flavonoids as major bioactive constituents of *N. nucifera*. These compounds have been shown to inhibit oxidative stress and neuroinflammatory signaling pathways involved in the progression of neurodegenerative diseases (You et al., 2018; Zhang et al., 2025). The substantial reduction in TNF-α and IL-1β production observed following treatment with *N. nucifera* extract indicates effective suppression of inflammatory responses induced by LPS stimulation. Since both cytokines are central mediators of neuroinflammation and neuronal injury, their inhibition suggests a potential therapeutic role for lotus-derived phenolics in mitigating chronic inflammatory processes associated with Alzheimer's disease and Parkinson's disease (Li et al., 2024).

Microglial activation is a hallmark of neurodegenerative pathology, where persistent activation of the M1 phenotype contributes to excessive production of pro-inflammatory mediators, reactive oxygen species, and nitric oxide, ultimately leading to neuronal damage. In the present study, *N. nucifera* extract significantly reduced nitric oxide production and intracellular ROS accumulation. These findings indicate that the extract effectively attenuates oxidative stress, which is recognized as a major contributor to neuronal dysfunction and neurodegeneration.

Similar observations have been reported for flavonoid-rich botanical extracts, where suppression of oxidative stress was associated with enhanced neuronal survival and reduced inflammatory damage (Azlan et al., 2023; Subedi et al., 2017).

The inhibition of inflammatory signaling pathways further supports the neuroprotective activity of the extract. The observed downregulation of NF-κB p65, phosphorylated p38 MAPK, phosphorylated JNK, COX-2, and iNOS suggests that *N. nucifera* interferes with key molecular mechanisms responsible for sustaining neuroinflammation. Activation of NF-κB and MAPK pathways is known to promote the transcription of pro-inflammatory genes and amplify cytokine production in activated microglia. Therefore, suppression of these pathways can effectively disrupt the inflammatory cascade and limit neuronal injury (Hong et al., 2014; Katola & Olajide, 2023). The reduction in p38 MAPK and JNK phosphorylation observed in the

present study also agrees with previous reports demonstrating the ability of quercetin and myricetin to inhibit stress-activated kinases and prevent inflammatory signaling (You et al., 2018; Zhang et al., 2019).

An important finding of this investigation was the ability of *N. nucifera* extract to modulate microglial polarization. Treatment significantly reduced the expression of M1 markers, including iNOS and CD86, while enhancing the expression of M2 markers such as Arg-1, CD206, IL-4, and IL-10. This shift from a pro-inflammatory M1 phenotype toward an anti-inflammatory M2 phenotype is considered a critical mechanism for resolving neuroinflammation and promoting tissue repair. Enhanced production of IL-4 and IL-10 may contribute to the suppression of inflammatory signaling and facilitate restoration of neuronal homeostasis. Similar polarization effects have been reported for several plant-derived polyphenols capable of regulating microglial activation and improving neuroimmune balance (Darwish et al., 2023; Figueira et al., 2017).

The neuroprotective mechanisms observed in this study are likely multifactorial and may involve interactions among several signaling pathways. Inhibition of NF-κB signaling can reduce the expression of inflammatory cytokines and inducible nitric oxide synthase, whereas suppression of MAPK signaling may prevent activation of transcription factors involved in chronic inflammatory responses. Simultaneously, the antioxidant properties of the phenolic compounds may activate cytoprotective pathways such as Nrf2/ARE, enhancing cellular defense against oxidative stress. Previous studies have also suggested that flavonoids can activate SIRT1/AMPK signaling and inhibit TLR4-mediated inflammatory responses, thereby providing additional neuroprotection (Maurya et al., 2021; Kim et al., 2018). Collectively, these mechanisms contribute to the restoration of microglial homeostasis and protection of neuronal integrity.

The unique ecological conditions of Manipur may also influence the biosynthesis and accumulation of bioactive metabolites in *N. nucifera*. Environmental factors such as altitude, temperature, soil composition, and water quality can alter secondary metabolite production, resulting in region-specific phytochemical profiles with distinct biological activities. The relatively high abundance of flavonoids observed in the present study suggests that Manipur-derived lotus populations may represent valuable sources of neuroprotective phytochemicals. Further comparative studies involving lotus populations from different geographical regions would help clarify the influence of environmental factors on metabolite accumulation and therapeutic efficacy.

Overall, the findings provide evidence that *N. nucifera* possesses significant neuroprotective activity through the combined suppression of inflammatory cytokines, oxidative stress, and microglial activation. The ability of the extract to target multiple pathological pathways simultaneously supports its potential application as a natural therapeutic agent for the prevention and management of neurodegenerative disorders.

5. Conclusion

The present study demonstrated that *Nelumbo nucifera* collected from Manipur is a rich source of phenolic compounds, particularly myricetin and quercetin, which contribute substantially to its neuroprotective properties. The extract exhibited significant anti-inflammatory and antioxidant activities by reducing the production of TNF-α, IL-1β, nitric oxide, and reactive oxygen species in LPS-stimulated BV2 microglial cells. Furthermore, the extract effectively suppressed the activation of NF-κB, p38 MAPK, and JNK signaling pathways while promoting a phenotypic shift of microglia from the pro-inflammatory M1 state to the anti-inflammatory M2 state.

These findings suggest that *N. nucifera* exerts neuroprotective effects through multiple complementary mechanisms involving the regulation of inflammatory signaling, oxidative stress, and microglial polarization. The study provides a scientific basis for the traditional use of lotus and highlights the therapeutic potential of Manipur-derived *N. nucifera* as a natural source of bioactive compounds for the management of neuroinflammatory and neurodegenerative disorders. Future investigations involving in vivo studies, mechanistic validation, and clinical evaluation are warranted to further establish its efficacy and translational potential in neurodegenerative disease management.

Conflict of interest: The authors declare that they have no competing interests.

Funding: No funding has been received.

Ethics approval: Not Applicable. The research work and the report were made in an ethical and responsible manner.

Consent to participate: Not Applicable.

Consent for publication: Not Applicable.

Availability of data and Material: The datasets used and analysed during the current study are available from the authors on reasonable request. The datasets generated and used in our present study are included in this article.

References

1. Adhikary, K., Ganguly, K., Sarkar, R., Abubakar, Md., Banerjee, P., & Karak, P. (2025). Phytonutrients and their neuroprotective role in brain disorders. *Frontiers in Molecular Biosciences*, *12*, 1607330–1607330. https://doi.org/10.3389/fmolb.2025.1607330
2. Adhikary, K., Prameela, G., Das, J., Ramzan, M., Ganguly, K., Datta, N., Banerjee, P., Barman, S., Sridhar, S. B., Taj, T., Mondal, M., Ashique, S., Chopra, S., & Chopra, H. (2026). Phyto micronutrients in neurodegeneration: modulating microglial dynamics for neuroprotection. *Zeitschrift Für Naturforschung C*. https://doi.org/10.1515/znc-2025-0239

3. Ahsan, A. U., Sharma, V. L., Wani, A., & Chopra, M. (2020). Naringenin Upregulates AMPK-Mediated Autophagy to Rescue Neuronal Cells From β-Amyloid (1–42) Evoked Neurotoxicity. *Molecular Neurobiology*, *57*(8), 3589–3602. https://doi.org/10.1007/s12035-020-01969-4
4. Akkol, E. K., Çankaya, İ. T., Karatoprak, G. Ş., Çarpar, E., Sobarzo-Sánchez, E., & Capasso, R. (2021). Natural Compounds as Medical Strategies in the Prevention and Treatment of Psychiatric Disorders Seen in Neurological Diseases. *Frontiers in Pharmacology*, *12*, 669638–669638. https://doi.org/10.3389/fphar.2021.669638
5. Aktary, N., Jeong, Y. J., Oh, S.-S., Shin, Y. H., Sung, Y.-H., Rahman, M. M., Santiago, L. R., Choi, J., Song, H. G., Nurkolis, F., Ribeiro, R. I. M. de A., Park, M. N., & Kim, B. (2025). Unveiling the therapeutic potential of natural products in Alzheimer's disease: insights from in vitro, in vivo, and clinical studies. *Frontiers in Pharmacology*, *16*, 1601712–1601712. https://doi.org/10.3389/fphar.2025.1601712
6. Akyürek, T. U., Şenol, F. S., Süntar, İ., Eren, G., Ulutaş, O. K., & Orhan, İ. E. (2025). 3-Hydroxytyrosol as a phenolic cholinesterase inhibitor with antiamnesic activity: a multimethodological study of selected plant phenolics. *Frontiers in Pharmacology*, *16*, 1640034–1640034. https://doi.org/10.3389/fphar.2025.1640034
7. Alhawarri, M. B., Al-Thiabat, M. G., Dubey, A., Tufail, A., Fouad, D., Alrimawi, B. H., & Dayoob, M. (2024). ADME profiling, molecular docking, DFT, and MEP analysis reveal cissamaline, cissamanine, and cissamdine from Cissampelos capensis L.f. as potential anti-Alzheimer's agents. *RSC Advances*, *14*(14), 9878–9891. https://doi.org/10.1039/d4ra01070a
8. Ali, M. A. (2023). Neurological potency of native plants from sub-Himalayan West Bengal through reverse pharmacology. *Bioinformation*, *19*(10), 995–998. https://doi.org/10.6026/97320630019995
9. Ansari, H., Singh, K., Chauhan, S., Mishra, M. K., Mehta, N., Patel, E., Patani, P., Shah, B., Bagewadi, H., Vaidya, S., Golwala, D., Patel, D., Sahoo, S., Saleem, U., Chauhdary, Z., Raza, Z., Shah, S., Rahman, M., Zaib, P., … Bruce, B. (2022). Effect of Nelumbo nucifera rhizome extract in haloperidol induced Parkinson rat model. *Journal of Pharmaceutical Negative Results*, *13*. https://doi.org/10.47750/pnr.2022.13.s02.1
10. Atoki, A. V., Aja, P. M., Ondari, E. N., & Shinkafi, T. S. (2023). Advances in Alzheimer's disease therapeutics: biochemistry, exploring bioactive compounds and novel approaches. *International Journal of Food Properties*, *26*(1), 2091–2127. https://doi.org/10.1080/10942912.2023.2243050
11. Azam, S., Jakaria, Md., Kim, I., Kim, J.-S., Haque, Md. E., & Choi, D. (2019). Regulation of Toll-Like Receptor (TLR) Signaling Pathway by Polyphenols in the Treatment of Age-Linked Neurodegenerative Diseases: Focus on TLR4 Signaling. *Frontiers in Immunology*, *10*, 1000–1000. https://doi.org/10.3389/fimmu.2019.01000
12. Azlan, U. K., Annuar, N. A. K., Mediani, A., Aizat, W. M., Damanhuri, H. A., Tong, X., Yanagisawa, D., Tooyama, I., Ngah, W. Z. W., Jantan, I., & Hamezah, H. S. (2023). An insight into the neuroprotective and anti-neuroinflammatory effects and mechanisms of Moringa oleifera. *Frontiers in Pharmacology*, *13*, 1035220–1035220. https://doi.org/10.3389/fphar.2022.1035220
13. Baptista, F. I., Henriques, A. G., Silva, A. M. S., Wiltfang, J., & Silva, O. A. B. da C. e. (2013). Flavonoids as Therapeutic Compounds Targeting Key Proteins Involved in Alzheimer's Disease. *ACS Chemical Neuroscience*, *5*(2), 83–92. https://doi.org/10.1021/cn400213r
14. Barbalho, S. M., Boaro, B. L., Oliveira, J. da S. C., Patočka, J., Lamas, C. B., Tanaka, M., & Laurindo, L. F. (2025). Molecular Mechanisms Underlying Neuroinflammation Intervention with Medicinal Plants: A Critical and Narrative Review of the Current Literature. *Pharmaceuticals*, *18*(1), 133–133. https://doi.org/10.3390/ph18010133
15. Basurto-Islas, G., Díaz, M., Ocampo, L. M. Z., Martínez-Herrera, M., & López-Camacho, P. Y. (2025). Natural products against tau hyperphosphorylation-induced aggregates: Potential therapies for Alzheimer's disease. *Archiv Der Pharmazie*, *358*(1). https://doi.org/10.1002/ardp.202400721
16. Bhat, B. A., Almilaibary, A., Mir, R. A., Aljarallah, B., Mir, W. R., Ahmad, F., & Mir, M. A. (2022). Natural Therapeutics in Aid of Treating Alzheimer's Disease: A Green Gateway Toward Ending Quest for Treating Neurological Disorders. *Frontiers in Neuroscience*, *16*, 884345–884345. https://doi.org/10.3389/fnins.2022.884345
17. Bhat, S., Joghee, S., & Meenakshi, S. (2023). The Therapeutic Potential of Nelumbo nucifera: A Comprehensive Review of Its Phytochemistry and Medicinal Properties. *International Journal of Health & Allied Sciences*, *12*(4). https://doi.org/10.55691/2278-344x.1059
18. Bhattacharya, R. S., Singh, R., Panghal, A., Thakur, A., Singh, L., Verma, R. K., Singh, C., Goyal, M., & Kumar, J. (2025). Multi-Targeting Phytochemicals for Alzheimer's Disease. *Phytotherapy Research*, *39*(3), 1453–1483. https://doi.org/10.1002/ptr.8435
19. Book, A. (2024). Abstract Book. *International Journal of Applied Pharmaceutics*. https://doi.org/10.22159/ijap.2025v17i1.53183
20. Bordoloi, S., Pathak, K., Devi, M., Saikia, R., Das, J., Kashyap, V. H., Das, D., Ahmad, M. Z., & Abdel-Wahab, B. A. (2024). Some promising medicinal plants used in Alzheimer's disease: an ethnopharmacological perspective. *Discover Applied Sciences*, *6*(5). https://doi.org/10.1007/s42452-024-05811-7

21. Calderaro, A., Patanè, G. T., Tellone, E., Barreca, D., Ficarra, S., Misiti, F., & Laganà, G. (2022). The Neuroprotective Potentiality of Flavonoids on Alzheimer's Disease. *International Journal of Molecular Sciences*, *23*(23), 14835–14835. https://doi.org/10.3390/ijms232314835
22. Chakraborty, B., Mukerjee, N., Maitra, S., Zehravi, M., Mukherjee, D., Ghosh, A., Massoud, E. E. S., & Rahman, Md. H. (2022). Therapeutic Potential of Different Natural Products for the Treatment of Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity*, *2022*(1), 6873874–6873874. https://doi.org/10.1155/2022/6873874
23. Chen, G., Zhu, M., & Guo, M. (2019). Research advances in traditional and modern use of Nelumbo nucifera: phytochemicals, health promoting activities and beyond. *Critical Reviews in Food Science and Nutrition*, *59*. https://doi.org/10.1080/10408398.2018.1553846
24. Chen, Y., Peng, F., Xing, Z., Chen, J., Peng, C., & Li, D. (2022). Beneficial effects of natural flavonoids on neuroinflammation. *Frontiers in Immunology*, *13*, 1006434–1006434. https://doi.org/10.3389/fimmu.2022.1006434
25. Chen, Y., & Yu, Y. (2023). Tau and neuroinflammation in Alzheimer's disease: interplay mechanisms and clinical translation. *Journal of Neuroinflammation*, *20*(1), 165–165. https://doi.org/10.1186/s12974-023-02853-3
26. Chen, Z., Wang, X., Du, S., Liu, Q., Xu, Z., Guo, Y., & Lin, X. (2024). A review on traditional Chinese medicine natural products and acupuncture intervention for Alzheimer's disease based on the neuroinflammatory. *Chinese Medicine*, *19*(1), 35–35. https://doi.org/10.1186/s13020-024-00900-6
27. Chen, Z., Yan, L., Wang, Y., Wang, Q., Yu, L., & Liu, J. (2025). Natural Products Targeting Tau Protein Phosphorylation: A Promising Therapeutic Avenue for Alzheimer's Disease. *Planta Medica*, *91*(8), 386–408. https://doi.org/10.1055/a-2536-8919
28. Chheng, C., Waiwut, P., Plekratoke, K., Chulikhit, Y., Daodee, S., Monthakantirat, O., Pitiporn, S., Musigavong, N., Kwankhao, P., & Boonyarat, C. (2020). Multitarget Activities of Kleeb Bua Daeng, a Thai Traditional Herbal Formula, Against Alzheimer's Disease. *Pharmaceuticals*, *13*(5), 79–79. https://doi.org/10.3390/ph13050079
29. Choo, J. H., Lee, S. Y., Min, K., & Kang, N. G. (2025). Chemical Composition and Bioactivity of Nelumbo nucifera Gaertn. Flower Extract Fractions: In Vitro Antioxidant and Anti-Inflammatory Properties. *Current Issues in Molecular Biology*, *47*(12), 1065–1065. https://doi.org/10.3390/cimb47121065
30. Corbi, G., Conti, V., Davinelli, S., Scapagnini, G., Filippelli, A., & Ferrara, N. (2016). Dietary Phytochemicals in Neuroimmunoaging: A New Therapeutic Possibility for Humans? *Frontiers in Pharmacology*, *7*, 364–364. https://doi.org/10.3389/fphar.2016.00364
31. Darwish, S. F., Elbadry, A. M. M., Elbokhomy, A. S., Salama, G. A., & Salama, R. M. (2023). The dual face of microglia (M1/M2) as a potential target in the protective effect of nutraceuticals against neurodegenerative diseases. *Frontiers in Aging*, *4*, 1231706–1231706. https://doi.org/10.3389/fragi.2023.1231706
32. Das, B., Bhardwaj, P. K., Sharma, N., Sarkar, A., Haldar, P. K., & Mukherjee, P. K. (2023). Evaluation of Mollugo oppositifolia Linn. as cholinesterase and β-secretase enzymes inhibitor. *Frontiers in Pharmacology*, *13*, 990926–990926. https://doi.org/10.3389/fphar.2022.990926
33. Davinelli, S., Maes, M., Corbi, G., Zarrelli, A., Willcox, D. C., & Scapagnini, G. (2016). Dietary phytochemicals and neuro-inflammaging: from mechanistic insights to translational challenges. *Immunity & Ageing*, *13*(1), 16–16. https://doi.org/10.1186/s12979-016-0070-3
34. Demerdash, M., Attia, R. T., El-Sherei, M. M., Aziz, W. M. W. A., Fahmy, S. A., & Issa, M. Y. (2024). Unveiling the functional components and anti-Alzheimer's activity of Koelreuteria elegans (Seem.) A.C. Sm. using UHPLC-MS/MS and molecular networking. *Materials Advances*, *5*(8), 3432–3449. https://doi.org/10.1039/d4ma00007b
35. Dubey, S., & Baghel, S. S. (2019). Phytochemical investigation and determination of phytoconstituents in flower extract of Nelumbo nucifera. *Journal of Drug Delivery and Therapeutics*, *9*(1), 146–149. https://doi.org/10.22270/jddt.v9i1.2197
36. Farooqui, T., & Farooqui, A. A. (2017). *Summary and Perspective* (pp. 581–594). https://doi.org/10.1002/9781119155195.ch29
37. Figueira, I., Garcia, G., Pimpão, R. C., Terrasso, A. P., Costa, I. G. M., Almeida, A. F., Tavares, L., Pais, T. F., Pinto, P., Ventura, M. R., Filipe, A., McDougall, G. J., Stewart, D., Kim, K., Palmela, I., Brites, D., Brito, M. A., Brito, C., & Santos, C. N. dos. (2017). Polyphenols journey through blood-brain barrier towards neuronal protection. *Scientific Reports*, *7*(1), 11456–11456. https://doi.org/10.1038/s41598-017-11512-6
38. Gadakh, A. S., & Kulkarni, A. D. (2025). In-vitro Anti-inflammatory Potential of Nelumbo nucifera Rhizomes. *Journal of Pharma Insights and Research.*, *3*(1), 17–22. https://doi.org/10.69613/6ms67644
39. Ghosh, S., Debnath, I., Bhunia, S., Nandi, S., Ashique, S., Nayak, A., Mallick, S., & Basak, S. (2025). Decoding natural products for neuroprotection: Pathway networks and structural insights for drug development. *Chinese Herbal Medicines*, *17*(4), 643–672. https://doi.org/10.1016/j.chmed.2025.09.005
40. Hannan, Md. A., Dash, R., Sohag, A. A. M., Haque, Md. N., & Moon, I. S. (2020). Neuroprotection Against Oxidative Stress: Phytochemicals Targeting TrkB Signaling and the Nrf2-ARE Antioxidant System. *Frontiers in*

Molecular Neuroscience, *13*, 116–116. https://doi.org/10.3389/fnmol.2020.00116

41. He, S., Wang, C., Shi, W., Zhou, C., Liu, C., Xu, Y., Gui, Y., Jiang, X., & Fan, G. (2025). Assessment of the Properties and Mechanism of Three Lotus (Nelumbo nucifera Gaertn.) Parts for Sleep Improvement. *Chemistry & Biodiversity*, *22*(6). https://doi.org/10.1002/cbdv.202402788
42. Hole, K. L., & Williams, R. J. (2020). Flavonoids as an Intervention for Alzheimer's Disease: Progress and Hurdles Towards Defining a Mechanism of Action . *Brain Plasticity*, *6*(2), 167–192. https://doi.org/10.3233/bpl-200098
43. Hong, Z., Shi, X., Zhu, K., Wu, T., & Zhu, Y. Z. (2014). SCM-198 inhibits microglial overactivation and attenuates Aβ1-40-induced cognitive impairments in rats via JNK and NF-κB pathways. *Journal of Neuroinflammation*, *11*(1), 147–147. https://doi.org/10.1186/s12974-014-0147-x
44. Hornedo-Ortega, R., Cerezo, A. B., Pablos, R. M. de, Krisa, S., Richard, T., García-Parrilla, M. C., & Troncoso, A. M. (2018). Phenolic Compounds Characteristic of the Mediterranean Diet in Mitigating Microglia-Mediated Neuroinflammation. *Frontiers in Cellular Neuroscience*, *12*, 373–373. https://doi.org/10.3389/fncel.2018.00373
45. Ibrahim, W. W., Sayed, R. H., Abdelhameed, M. F., Omara, E. A., Nassar, M. I., Abdelkader, N. F., Farag, M. A., Elshamy, A. I., & Afifi, S. M. (2024). Neuroprotective potential of Erigeron bonariensis ethanolic extract against ovariectomized/D-galactose-induced memory impairments in female rats in relation to its metabolite fingerprint as revealed using UPLC/MS. *Inflammopharmacology*, *32*(2), 1091–1112. https://doi.org/10.1007/s10787-023-01418-3
46. Iqubal, A., Rahman, S. O., Ahmed, M., Bansal, P., Haider, M. R., Iqubal, M. K., Najmi, A. K., Pottoo, F. H., & Haque, S. E. (2020). 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*(6), 685–720. https://doi.org/10.2174/1389450121999201209201004
47. Jalouli, M., Rahman, Md. A., Biswas, P., Rahman, MD. H., Harrath, A. H., Lee, I.-S., Kang, S., Choi, J., Park, M. N., & Kim, B. (2025). Targeting natural antioxidant polyphenols to protect neuroinflammation and neurodegenerative diseases: a comprehensive review. *Frontiers in Pharmacology*, *16*, 1492517–1492517. https://doi.org/10.3389/fphar.2025.1492517
48. Jang, J.-H., Lee, S. H., Jung, K., Yoo, H., & Park, G. (2020). Inhibitory Effects of Myricetin on Lipopolysaccharide-Induced Neuroinflammation. *Brain Sciences*, *10*(1), 32–32. https://doi.org/10.3390/brainsci10010032
49. Jarmkom, K., Techaoei, S., Wisidsri, N., & Khobjai, W. (2019). EVALUATION OF ACETYLCHOLINESTERASE ACTIVITY AND CYTOTOXICITY OF DIFFERENT PARTS OF NELUMBO NUCIFERA GAERTN ON HUMAN NEUROBLASTOMA CELL LINE (SH-SY5Y). *International Journal of Applied Pharmaceutics*, 103–105. https://doi.org/10.22159/ijap.2019.v11s5.t0080
50. Jung, H. A., Jung, Y. J., Hyun, S. K., Min, B. S., Kim, D., Jung, J. H., & Choi, J. S. (2010). Selective Cholinesterase Inhibitory Activities of a New Monoterpene Diglycoside and Other Constituents from Nelumbo nucifera Stamens. *Biological and Pharmaceutical Bulletin*, *33*(2), 267–272. https://doi.org/10.1248/bpb.33.267
51. Katola, F. O., & Olajide, O. A. (2022). Nimbolide targets multiple signalling pathways to reduce neuroinflammation in BV2 microglia. In *Research Square*. https://doi.org/10.21203/rs.3.rs-2202062/v1
52. Katola, F. O., & Olajide, O. A. (2023). Nimbolide Targets Multiple Signalling Pathways to Reduce Neuroinflammation in BV-2 Microglia. *Molecular Neurobiology*, *60*(9), 5450–5467. https://doi.org/10.1007/s12035-023-03410-y
53. Khayatan, D., Razavi, S. M., Arab, Z. N., Khanahmadi, M., Samanian, A., Momtaz, S., Sukhorukov, V. N., Jamialahmadi, T., Abdolghaffari, A. H., Barreto, G. E., & Sahebkar, A. (2024). Protective Effects of Plant-Derived Compounds Against Traumatic Brain Injury. *Molecular Neurobiology*, *61*(10), 7732–7750. https://doi.org/10.1007/s12035-024-04030-w
54. Khobjai, W., Wisidsri, N., Jarmkom, K., & Techaoei, S. (2021). PHYTOCHEMICAL COMPOSITION AND ANTIINFLAMMATORY ACTIVITY OF NELUMBO NUCIFERA GAERTN. *International Journal of Applied Pharmaceutics*, 42–46. https://doi.org/10.22159/ijap.2021.v13s1.y0102
55. Kim, B.-W., Koppula, S., Hong, S., Jeon, S., Kwon, J., Hwang, B., Park, E., & Choi, D. (2013). Regulation of Microglia Activity by Glaucocalyxin-A: Attenuation of Lipopolysaccharide-Stimulated Neuroinflammation through NF-κB and p38 MAPK Signaling Pathways. *PLoS ONE*, *8*(2). https://doi.org/10.1371/journal.pone.0055792
56. Kim, K.-W., Shin, W. C., Jang, J., Kim, M., Yoon, D., Lee, Y., & Lee, D. (2025). Metabolic profiling and anti-neuroinflammatory effects of Liriope platyphylla extract in LPS-stimulated BV2 microglia. *Applied Biological Chemistry*, *68*(1). https://doi.org/10.1186/s13765-025-01015-8
57. Kim, S., Jin, C., Kim, C., Yoo, Y. H., Choi, S. H., Kim, G., Yoon, H. J., Park, H., & Choi, Y. H. (2018). Isorhamnetin alleviates lipopolysaccharide-induced inflammatory responses in BV2 microglia by inactivating NF-κB, blocking the TLR4 pathway and reducing ROS generation. *International Journal of Molecular Medicine*, *43*(2), 682–692. https://doi.org/10.3892/ijmm.2018.3993

58. Kruszka, J., Martyński, J., Szewczyk-Golec, K., Woźniak, A., & Nuszkiewicz, J. (2025). The Role of Selected Flavonoids in Modulating Neuroinflammation in Alzheimer's Disease: Mechanisms and Therapeutic Potential. *Brain Sciences*, *15*(5), 485–485. https://doi.org/10.3390/brainsci15050485
59. Kumar, Gp., & Khanum, F. (2012). Neuroprotective potential of phytochemicals. *Pharmacognosy Reviews/Bioinformatics Trends/Pharmacognosy Review*, *6*(12), 81–81. https://doi.org/10.4103/0973-7847.99898
60. Kumaran, A., Ho, C. C., & Hwang, L. S. (2017). Protective effect of Nelumbo nucifera extracts on beta amyloid protein induced apoptosis in PC12 cells, in vitro model of Alzheimer's disease. *Journal of Food and Drug Analysis*, *26*(1), 172–181. https://doi.org/10.1016/j.jfda.2017.01.007
61. Kumaree, K. K., Brimson, J. M., Verma, K., Chuchawankul, S., Tencomnao, T., & Prasansuklab, A. (2025). Agarwood leaf ethanol extract provides neuroprotective properties and promotes cholinergic differentiation of HT22 hippocampal neurons. *Scientific Reports*, *15*(1), 10230–10230. https://doi.org/10.1038/s41598-025-93462-y
62. Lai, Z., Ke, L., & Zhao, W. (2025). Naringenin as a neurotherapeutic agent in Alzheimer's disease: epigenetic signatures, gut microbiota alterations, and molecular neuroprotection. *Frontiers in Aging Neuroscience*, *17*, 1647967–1647967. https://doi.org/10.3389/fnagi.2025.1647967
63. Larson, K. C., Martens, L. H., Marconi, M., Dejesus, C., Bruhn, S., Miller, T. A., Tate, B., & Levenson, J. M. (2024). Preclinical translational platform of neuroinflammatory disease biology relevant to neurodegenerative disease. *Journal of Neuroinflammation*, *21*(1), 37–37. https://doi.org/10.1186/s12974-024-03029-3
64. Laurindo, L. F., Dias, J. A., Araújo, A. C., Pomini, K. T., Galhardi, C. M., Detregiachi, C. R. P., Haber, L. S. de A., Roque, D. D., Bechara, M. D., Castro, M. V. M. de, Pereira, E. de S. B. M., Tofano, R. J., Borgo, I. J. S. G., & Barbalho, S. M. (2024). Immunological dimensions of neuroinflammation and microglial activation: exploring innovative immunomodulatory approaches to mitigate neuroinflammatory progression. *Frontiers in Immunology*, *14*, 1305933–1305933. https://doi.org/10.3389/fimmu.2023.1305933
65. Lee, J., Jo, D., Park, D., Chung, H. Y., & Mattson, M. P. (2014). Adaptive Cellular Stress Pathways as Therapeutic Targets of Dietary Phytochemicals: Focus on the Nervous System. *Pharmacological Reviews*, *66*(3), 815–868. https://doi.org/10.1124/pr.113.007757
66. Li, D., Fan, H., Yang, R., Li, Y., Zhang, F., & Shi, J. (2022). Dendrobium Nobile Lindl. Alkaloid Suppresses NLRP3-Mediated Pyroptosis to Alleviate LPS-Induced Neurotoxicity. *Frontiers in Pharmacology*, *13*, 846541–846541. https://doi.org/10.3389/fphar.2022.846541
67. Li, J., Xiang, H., Huang, C., & Lu, J. (2021). Pharmacological Actions of Myricetin in the Nervous System: A Comprehensive Review of Preclinical Studies in Animals and Cell Models. *Frontiers in Pharmacology*, *12*, 797298–797298. https://doi.org/10.3389/fphar.2021.797298
68. Li, Z., Wu, W., Liu, R., Niu, B., Chen, H., Chen, H., Shentu, X., Gao, H., Chen, H., & Chen, H. (2024). Flavonoid profiling of Plumula nelumbinis and evaluation of their anti-inflammatory effects on lipopolysaccharide-induced RAW 264.7 macrophages. *eFood*, *5*(4). https://doi.org/10.1002/efd2.150
69. Lim, D. W., Lee, J., Lee, C.-H., & Kim, Y. T. (2024). Natural Products and Their Neuroprotective Effects in Degenerative Brain Diseases: A Comprehensive Review. *International Journal of Molecular Sciences*, *25*(20), 11223–11223. https://doi.org/10.3390/ijms252011223
70. Lim, H.-S., Kim, Y. J., Kim, B., Park, G., & Jeong, S. (2018). The Anti-neuroinflammatory Activity of Tectorigenin Pretreatment via Downregulated NF-κB and ERK/JNK Pathways in BV-2 Microglial and Microglia Inactivation in Mice With Lipopolysaccharide. *Frontiers in Pharmacology*, *9*, 462–462. https://doi.org/10.3389/fphar.2018.00462
71. Limwachiranon, J., Huang, H., Shi, Z., Li, L., & Luo, Z. (2018). Lotus Flavonoids and Phenolic Acids: Health Promotion and Safe Consumption Dosages. *Comprehensive Reviews in Food Science and Food Safety*, *17*(2), 458–471. https://doi.org/10.1111/1541-4337.12333
72. Liu, J., Li, T., Zhong, G., Pan, Y., Gao, M., Su, S., Liang, Y., Ma, C., Liu, Y., Wang, Q., & Shi, Q. (2023). Exploring the therapeutic potential of natural compounds for Alzheimer's disease: Mechanisms of action and pharmacological properties. *Biomedicine & Pharmacotherapy*, *166*, 115406–115406. https://doi.org/10.1016/j.biopha.2023.115406
73. Liu, S., Lu, T.-H., Su, C., Lay, I., Lin, H., Fang, K., Ho, T.-J., Chen, K., Su, Y., Chiang, W., & Chen, Y. (2014). Lotus Leaf (Nelumbo nucifera) and its Active Constituents Prevent Inflammatory Responses in Macrophages via JNK/NF-κB Signaling Pathway. *The American Journal of Chinese Medicine*, *42*(4), 869–889. https://doi.org/10.1142/s0192415x14500554
74. Liu, W., Ma, H., DaSilva, N. A., Rose, K. N., Johnson, S. L., Zhang, L., Wan, C., Dain, J. A., & Seeram, N. P. (2016). Development of a neuroprotective potential algorithm for medicinal plants. *Neurochemistry International*, *100*, 164–177. https://doi.org/10.1016/j.neuint.2016.09.014
75. Liu, Y., Xu, X., Wu, X.-M., Yang, G., Luo, J., Liang, X., Chen, J., & Li, Y. (2025). TMF Attenuates Cognitive Impairment and Neuroinflammation by Inhibiting the MAPK/NF-κB Pathway in Alzheimer's Disease: A Multi-

Omics Analysis. *Marine Drugs*, *23*(2), 74–74. https://doi.org/10.3390/md23020074

76. Lo, T. Y., Chan, A. S. L., Cheung, S. T., Yung, L. Y., Leung, M. M. H., & Wong, Y. H. (2023). Multi-target regulatory mechanism of Yang Xin Tang − a traditional Chinese medicine against dementia. *Chinese Medicine*, *18*(1), 101–101. https://doi.org/10.1186/s13020-023-00813-w
77. Malik, I., Afzal, S., & Attiq, A. (2026). *Neurodegenerative Natural Foes* (pp. 391–418). https://doi.org/10.4018/979-8-3373-4139-2.ch014
78. Mamun, A. A., Shao, C., Geng, P., Wang, S., & Xiao, J. (2024). Polyphenols Targeting NF-κB Pathway in Neurological Disorders: What We Know So Far? *International Journal of Biological Sciences*, *20*(4), 1332–1355. https://doi.org/10.7150/ijbs.90982
79. Mathew, M., & Subramanian, S. (2014). In Vitro Screening for Anti-Cholinesterase and Antioxidant Activity of Methanolic Extracts of Ayurvedic Medicinal Plants Used for Cognitive Disorders. *PLoS ONE*, *9*(1). https://doi.org/10.1371/journal.pone.0086804
80. Maurya, S. K., Bhattacharya, N., Mishra, S., Bhattacharya, A., Banerjee, P., Senapati, S., & Mishra, R. (2021). Microglia Specific Drug Targeting Using Natural Products for the Regulation of Redox Imbalance in Neurodegeneration. *Frontiers in Pharmacology*, *12*, 654489–654489. https://doi.org/10.3389/fphar.2021.654489
81. Meng, X., Zheng, L.-C., Liu, J., Gao, C., Qiu, M.-C., Liu, Y., Lu, J., Wang, D., & Chen, C.-L. (2017). Inhibitory effects of three bisbenzylisoquinoline alkaloids on lipopolysaccharide-induced microglial activation. *RSC Advances*, *7*(30), 18347–18357. https://doi.org/10.1039/c7ra01882g
82. Mitra, K., Raihan, M. A., Rahman, Md. A., Rouf, R., Reza, H. M., Uddin, S. J., & Muhammad, I. (2022). Therapeutic Potential of Nelumbo nucifera (Sacred Lotus) in CNS Disorders. *Dhaka University Journal of Pharmaceutical Sciences*, 347–358. https://doi.org/10.3329/dujps.v20i3.59800
83. Nahar, L., Charoensup, R., Kalieva, K., Habibi, E., Guo, M., Wang, D., Kvasnica, M., Önder, A., & Sarker, S. D. (2025). Natural products in neurodegenerative diseases: recent advances and future outlook. *Frontiers in Pharmacology*, *16*, 1529194–1529194. https://doi.org/10.3389/fphar.2025.1529194
84. Olajide, O. A., & Sarker, S. D. (2020). Alzheimer's disease: natural products as inhibitors of neuroinflammation. *Inflammopharmacology*, *28*(6), 1439–1455. https://doi.org/10.1007/s10787-020-00751-1
85. Oliveira, S. D., Andrade, E. H. de A., Kumar, R., & Mali, S. N. (2023). Medicinal Plants - Chemical, Biochemical, and Pharmacological Approaches. In *IntechOpen eBooks*. IntechOpen. https://doi.org/10.5772/intechopen.107682
86. On-Nom, N., Thangsiri, S., Inthachat, W., Temviriyanukul, P., Sahasakul, Y., Chupeerach, C., Pruesapan, K., Trisonthi, P., Siriwan, D., & Suttisansanee, U. (2023). Seasonal Effects on Phenolic Contents and In Vitro Health-Promoting Bioactivities of Sacred Lotus (Nelumbo nucifera). *Plants*, *12*(7), 1441–1441. https://doi.org/10.3390/plants12071441
87. On-Nom, N., Thangsiri, S., Inthachat, W., Temviriyanukul, P., Trisonthi, P., Chupeerach, C., Siriwan, D., & Suttisansanee, U. (2023). Phenolic profiles and in vitro biochemical properties of Thai herb ingredients for chronic diseases prevention. *Scientific Reports*, *13*(1), 21690–21690. https://doi.org/10.1038/s41598-023-49074-5
88. Othman, A., Sayed, A. M., Amen, Y., & Shimizu, K. (2022). Possible neuroprotective effects of amide alkaloids from Bassia indica and Agathophora alopecuroides: in vitro and in silico investigations. *RSC Advances*, *12*(29), 18746–18758. https://doi.org/10.1039/d2ra02275c
89. Park, E., Kim, G. D., Go, M.-S., Kwon, D., Jung, I.-K., Auh, J., & Kim, J. (2017). Anti-inflammatory effects ofNelumboleaf extracts and identification of their metabolites. *Nutrition Research and Practice*, *11*(4), 265–265. https://doi.org/10.4162/nrp.2017.11.4.265
90. Park, H. Y. (2012). Naringenin attenuates the release of pro-inflammatory mediators from lipopolysaccharide-stimulated BV2 microglia by inactivating nuclear factor-κB and inhibiting mitogen-activated protein kinases. *International Journal of Molecular Medicine*, *30*(1), 204–210. https://doi.org/10.3892/ijmm.2012.979
91. Park, H. Y., Park, C., Hwang, H. J., Kim, B. W., Kim, G., Kim, C. M., Kim, N. D., & Choi, Y. H. (2014). 7,8-Dihydroxyflavone attenuates the release of pro-inflammatory mediators and cytokines in lipopolysaccharide-stimulated BV2 microglial cells through the suppression of the NF-κB and MAPK signaling pathways. *International Journal of Molecular Medicine*, *33*(4), 1027–1034. https://doi.org/10.3892/ijmm.2014.1652
92. Park, S. Y., Choi, M. J., Park, G., & Choi, Y. W. (2017). Petasites japonicus bakkenolide B inhibits lipopolysaccharide-induced pro-inflammatory cytokines via AMPK/Nrf2 induction in microglia. *International Journal of Molecular Medicine*, *41*(3), 1683–1692. https://doi.org/10.3892/ijmm.2017.3350
93. Pavlov, S. A., Prajapati, S. K., Yadav, D., Marcano-Rodriguez, A., Yadav, H., & Jain, S. (2025). Advances in Bioactive Compounds from Plants and Their Applications in Alzheimer's Disease. *Biomolecules*, *16*(1), 7–7. https://doi.org/10.3390/biom16010007
94. Poonasri, M., Mankhong, S., Chiranthanut, N., & Srisook, K. (2023). 4-methoxycinnamyl p-coumarate reduces neuroinflammation by blocking NF-κB, MAPK, and Akt/GSK-3β pathways and enhancing Nrf2/HO-1 signaling cascade in microglial cells. *Biomedicine & Pharmacotherapy*,

168, 115808–115808. https://doi.org/10.1016/j.biopha.2023.115808

95. Puri, V., Kanojia, N., Sharma, A., Huanbutta, K., Dheer, D., & Sangnim, T. (2022). Natural product-based pharmacological studies for neurological disorders. *Frontiers in Pharmacology*, *13*, 1011740–1011740. https://doi.org/10.3389/fphar.2022.1011740
96. Qi, G., Mi, Y., Fan, R., Li, R., Liu, Z., & Liu, X. (2019). Nobiletin Protects against Systemic Inflammation-Stimulated Memory Impairment via MAPK and NF-κB Signaling Pathways. *Journal of Agricultural and Food Chemistry*, *67*(18), 5122–5134. https://doi.org/10.1021/acs.jafc.9b00133
97. Rehman, M. U., Wali, A. F., Ahmad, A., Shakeel, S., Rasool, S., Ali, R., Rashid, S. M., Madkhali, H., Ganaie, M. A., & Khan, R. (2018). Neuroprotective Strategies for Neurological Disorders by Natural Products: An update. *Current Neuropharmacology*, *17*(3), 247–267. https://doi.org/10.2174/1570159x16666180911124605
98. Sahakyan, N. (2025). Plant-derived phenolics as regulators of nitric oxide production in microglia: mechanisms and therapeutic potential. *Medical Gas Research*, *16*(2), 169–175. https://doi.org/10.4103/mgr.medgasres-d-25-00058
99. Sahebnasagh, A., Eghbali, S., Saghafi, F., García-Ríos, A., & Avan, R. (2022). Neurohormetic phytochemicals in the pathogenesis of neurodegenerative diseases. *Immunity & Ageing*, *19*(1), 36–36. https://doi.org/10.1186/s12979-022-00292-x
100. Salinaro, A. T., Pennisi, M., Paola, R. D., Scuto, M., Crupi, R., Cambria, M. T., Ontario, M. L., Tomasello, M., Uva, M. G., Maiolino, L., Calabrese, E. J., Cuzzocrea, S., & Calabrese, V. (2018). Neuroinflammation and neurohormesis in the pathogenesis of Alzheimer's disease and Alzheimer-linked pathologies: modulation by nutritional mushrooms. *Immunity & Ageing*, *15*(1), 8–8. https://doi.org/10.1186/s12979-017-0108-1
101. Sánchez-Martínez, J. D., Valdés, A., Gallego, R., Suárez-Montenegro, Z. J., Alarcón, M., Ibáñez, E., Álvarez-Rivera, G., & Cifuentes, A. (2022). Blood–Brain Barrier Permeability Study of Potential Neuroprotective Compounds Recovered From Plants and Agri-Food by-Products. *Frontiers in Nutrition*, *9*, 924596–924596. https://doi.org/10.3389/fnut.2022.924596
102. Santos, T. C. dos, Gomes, T. M., Pinto, B., Camara, A. L., & Paes, A. M. de A. (2018). Naturally Occurring Acetylcholinesterase Inhibitors and Their Potential Use for Alzheimer's Disease Therapy. *Frontiers in Pharmacology*, *9*, 1192–1192. https://doi.org/10.3389/fphar.2018.01192
103. Scapagnini, G., Vasto, S., Nader, A. G., Calogero, C., Zella, D., & Galvano, F. (2011). Modulation of Nrf2/ARE Pathway by Food Polyphenols: A Nutritional Neuroprotective Strategy for Cognitive and Neurodegenerative Disorders. *Nova Science Publishers (Nova Science Publishers, Inc.)*, *44*(2), 192–201. https://doi.org/10.1007/s12035-011-8181-5
104. Shal, B., Ding, W., Ali, H., Kim, Y. S., & Khan, S. (2018). Anti-neuroinflammatory Potential of Natural Products in Attenuation of Alzheimer's Disease. *Frontiers in Pharmacology*, *9*, 548–548. https://doi.org/10.3389/fphar.2018.00548
105. Sharifi-Rad, J., Rapposelli, S., Sestito, S., Herrera-Bravo, J., Arancibia-Díaz, A., Salazar, L. A., Yeskaliyeva, B., Beyatlı, A., Leyva-Gómez, G., González-Contreras, C., Gürer, E. S., Martorell, M., & Călina, D. (2022). Multi-Target Mechanisms of Phytochemicals in Alzheimer's Disease: Effects on Oxidative Stress, Neuroinflammation and Protein Aggregation. *Journal of Personalized Medicine*, *12*(9), 1515–1515. https://doi.org/10.3390/jpm12091515
106. Sharifi-Rad, M., Lankatillake, C., Dias, D. A., Docea, A. O., Mahomoodally, M. F., Lobine, D., Chazot, P. L., Kurt, B., Tumer, T. B., Moreira, A. C., Sharopov, F., Martorell, M., Martins, N., Cho, W. C., Călina, D., & Sharifi-Rad, J. (2020). Impact of Natural Compounds on Neurodegenerative Disorders: From Preclinical to Pharmacotherapeutics. *Journal of Clinical Medicine*, *9*(4), 1061–1061. https://doi.org/10.3390/jcm9041061
107. Sharma, B. R., Gautam, L. N. S., Adhikari, D., & Karki, R. (2016). A Comprehensive Review on Chemical Profiling of Nelumbo Nucifera: Potential for Drug Development. *Phytotherapy Research*, *31*(1), 3–26. https://doi.org/10.1002/ptr.5732
108. Shoaib, S., Ansari, M. A., Fatease, A. A., Safhi, A. Y., Hani, U., Jahan, R., Alomary, M. N., Ansari, M. N., Ahmed, N., Wahab, S., Ahmad, W., Yusuf, N., & Islam, N. (2023). Plant-Derived Bioactive Compounds in the Management of Neurodegenerative Disorders: Challenges, Future Directions and Molecular Mechanisms Involved in Neuroprotection. *Pharmaceutics*, *15*(3), 749–749. https://doi.org/10.3390/pharmaceutics15030749
109. Šimunková, M., Alwasel, S., Alhazza, I. M., Jomová, K., Kollár, V., Rusko, M., & Valko, M. (2019). Management of oxidative stress and other pathologies in Alzheimer's disease. *Archives of Toxicology*, *93*(9), 2491–2513. https://doi.org/10.1007/s00204-019-02538-y
110. Singh, B., Mahajan, S., Abdella, S., Khan, R., & Garg, S. (2025). Exploring Autophagy Inducing Molecules: Targeting Diverse Pathways in Alzheimer's Disease Management. *Medicinal Research Reviews*, *46*(1), 272–298. https://doi.org/10.1002/med.70013
111. Singh, D. (2022). Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. *Journal of Neuroinflammation*, *19*(1), 206–206. https://doi.org/10.1186/s12974-022-02565-0
112. Singhal, H. K., & Neetu. (2025). Exploring the Medicinal Wealth of Nelumbo nucifera Gaertn: A Review on its Traditional Uses and Scientific

Perspectives. *Journal of Complementary and Alternative Medical Research*, *26*(7), 189–198. https://doi.org/10.9734/jocamr/2025/v26i7685

113. Stojanović, T., Rakić, M., Ćosić, M. V., Pavlović, M. O., Sabovljević, A., Sabovljević, M., Božić, B., Nedeljković, B. B., Vujičić, M. M., & Lunić, T. (2025). Moss Extracts as Natural Neuroprotective Agents: Mitigating LPS-Induced Neuroinflammation and Microglial Activation. *Cells*, *14*(11), 780–780. https://doi.org/10.3390/cells14110780
114. Subedi, L., Kwon, O. W., Pak, C., Lee, G., Lee, K., Kim, H., & Kim, S. Y. (2017). N,N-disubstituted azines attenuate LPS-mediated neuroinflammation in microglia and neuronal apoptosis via inhibiting MAPK signaling pathways. *BMC Neuroscience*, *18*(1), 82–82. https://doi.org/10.1186/s12868-017-0399-3
115. Suganya*, M., Sangmeswaran, Prof. Dr. B., Preethi, A., Preethi, M., Priyadharshini, S., & Raaghul, R. (2025a). A REVIEW ON PHYTOCONSTITUENTS AND PHARMACOLOGICAL ACTIVITY OF NELUMBO NUCIFERA. *Zenodo (CERN European Organization for Nuclear Research)*. https://doi.org/10.5281/zenodo.17617660
116. Suganya*, M., Sangmeswaran, Prof. Dr. B., Preethi, A., Preethi, M., Priyadharshini, S., & Raaghul, R. (2025b). A REVIEW ON PHYTOCONSTITUENTS AND PHARMACOLOGICAL ACTIVITY OF NELUMBO NUCIFERA. *Zenodo (CERN European Organization for Nuclear Research)*. https://doi.org/10.5281/zenodo.17617661
117. Temviriyanukul, P., Chansawhang, A., Inthachat, W., Supasawat, P., Phochantachinda, S., Pitchakarn, P., & Chantong, B. (2024). Phikud navakot extract acts as an ER stress inhibitor to ameliorate ER stress and neuroinflammation. *PubMed Central*, *10*(21). https://doi.org/10.1016/j.heliyon.2024.e39700
118. Temviriyanukul, P., Sritalahareuthai, V., Promyos, N., Thangsiri, S., Pruesapan, K., Srinuanchai, W., Nuchuchua, O., Siriwan, D., On-Nom, N., & Suttisansanee, U. (2020). The Effect of Sacred Lotus (Nelumbo nucifera) and Its Mixtures on Phenolic Profiles, Antioxidant Activities, and Inhibitions of the Key Enzymes Relevant to Alzheimer's Disease. *Molecules*, *25*(16), 3713–3713. https://doi.org/10.3390/molecules25163713
119. Tripathi, P. N., Lodhi, A., Nand, S., Nandi, N., Dumoga, S., Yadav, P., Tiwari, A., Singh, S. K., El-Shorbagi, A., & Chaudhary, S. (2024). Review of Pharmacotherapeutic Targets in Alzheimer's Disease and Its Management Using Traditional Medicinal Plants. *Degenerative Neurological and Neuromuscular Disease*, 47–74. https://doi.org/10.2147/dnnd.s452009
120. Tseng, T., Liaw, C., Shiao, Y., Huang, Y.-I., Cheng, Y.-H., Chen, W.-C., & Tsai, K. (2025). NeuproGemp, a polyphenol-rich botanical formula, ameliorates Alzheimer's-like pathology in APP/PS1 mice via inhibition of human glutaminyl cyclase. *Frontiers in Pharmacology*, *16*, 1673532–1673532. https://doi.org/10.3389/fphar.2025.1673532
121. Tungmunnithum, D., Drouet, S., Garros, L., & Hano, C. (2022). Differential Flavonoid and Other Phenolic Accumulations and Antioxidant Activities of Nymphaea lotus L. Populations throughout Thailand. *Molecules*, *27*(11), 3590–3590. https://doi.org/10.3390/molecules27113590
122. Tungmunnithum, D., Drouet, S., & Hano, C. (2022). Phytochemical Diversity and Antioxidant Potential of Natural Populations of Nelumbo nucifera Gaertn. throughout the Floristic Regions in Thailand. *Molecules*, *27*(3), 681–681. https://doi.org/10.3390/molecules27030681
123. Tungmunnithum, D., Pinthong, D., & Hano, C. (2018). Flavonoids from Nelumbo nucifera Gaertn., a Medicinal Plant: Uses in Traditional Medicine, Phytochemistry and Pharmacological Activities. *Medicines*, *5*(4), 127–127. https://doi.org/10.3390/medicines5040127
124. Tyler, S. E. B., & Tyler, L. D. K. (2022). Therapeutic roles of plants for 15 hypothesised causal bases of Alzheimer's disease. *Natural Products and Bioprospecting*, *12*(1), 34–34. https://doi.org/10.1007/s13659-022-00354-z
125. Tyler, S. E. B., & Tyler, L. D. K. (2023). Reversing memory/cognitive impairment with medicinal plants targeting inflammation and its crosstalk with other pathologies. *Brain Disorders*, *11*, 100094–100094. https://doi.org/10.1016/j.dscb.2023.100094
126. Vauzour, D. (2012). Dietary Polyphenols as Modulators of Brain Functions: Biological Actions and Molecular Mechanisms Underpinning Their Beneficial Effects. *Oxidative Medicine and Cellular Longevity*, *2012*, 1–16. https://doi.org/10.1155/2012/914273
127. Vauzour, D., Martinsen, A., & Layé, S. (2015). Neuroinflammatory processes in cognitive disorders: Is there a role for flavonoids and n-3 polyunsaturated fatty acids in counteracting their detrimental effects? *Neurochemistry International*, *89*, 63–74. https://doi.org/10.1016/j.neuint.2015.08.004
128. Vauzour, D., Vafeiadou, K., Rodriguez-Mateos, A., Rendeiro, C., & Spencer, J. P. E. (2008). The neuroprotective potential of flavonoids: a multiplicity of effects. *Genes & Nutrition*, *3*, 115–126. https://doi.org/10.1007/s12263-008-0091-4
129. Velagapudi, R., El-Bakoush, A., & Olajide, O. A. (2018). Activation of Nrf2 Pathway Contributes to Neuroprotection by the Dietary Flavonoid Tiliroside. *Molecular Neurobiology*, *55*(10), 8103–8123. https://doi.org/10.1007/s12035-018-0975-2
130. Velagapudi, R., Jamshaid, F., Lepiarz-Raba, I., Katola, F. O., Hemming, K., & Olajide, O. A. (2019). The tiliroside derivative, 3-O-[(E)-(2-oxo-4-(p-tolyl) but–3–en–1–yl] kaempferol produced inhibition of neuroinflammation and activation of AMPK and Nrf2/HO-1 pathways in BV-2

microglia. *International Immunopharmacology*, *77*, 105951–105951. https://doi.org/10.1016/j.intimp.2019.105951

131. Wahid, M., Ali, A., Saqib, F., Aleem, A., Bibi, S., Afzal, K., Ali, A., Baig, A., Khan, S. A., & Asad, M. H. H. B. (2020). Pharmacological exploration of traditional plants for the treatment of neurodegenerative disorders. *Phytotherapy Research*, *34*(12), 3089–3112. https://doi.org/10.1002/ptr.6742
132. Wang, J., Bi, W., Cheng, A., Freire, D., Vempati, P., Zhao, W., Gong, B., Janle, E. M., Chen, T., Ferruzzi, M. G., Schmeidler, J., Ho, L., & Pasinetti, G. M. (2014). Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer's disease-experimental approach and therapeutic implications. *Frontiers in Aging Neuroscience*, *6*, 42–42. https://doi.org/10.3389/fnagi.2014.00042
133. Wang, J., Ferruzzi, M. G., Ho, L., Blount, J. W., Janle, E. M., Gong, B., Pan, Y., Gowda, G. A. N., Raftery, D., Arrieta-Cruz, I., Sharma, V., Cooper, B. R., Lobo, J., Simon, J. E., Zhang, C., Cheng, A., Qian, X., Ono, K., Teplow, D. B., … Pasinetti, G. M. (2012). Brain-Targeted Proanthocyanidin Metabolites for Alzheimer's Disease Treatment. *Journal of Neuroscience*, *32*(15), 5144–5150. https://doi.org/10.1523/jneurosci.6437-11.2012
134. Wang, Z., Li, Y., Ma, D., Zeng, M., Wang, Z., Qin, F., Chen, J., Christian, M., & He, Z. (2021). Alkaloids from lotus (Nelumbo nucifera): recent advances in biosynthesis, pharmacokinetics, bioactivity, safety, and industrial applications. *Critical Reviews in Food Science and Nutrition*, *63*(21), 4867–4900. https://doi.org/10.1080/10408398.2021.2009436
135. Wen, Y., Fu, H., Chen, Q., Lan, C., Qin, D., Wu, J., Wu, A., & Zhou, X. (2024). Exploring the therapeutic potential of Nelumbo nucifera leaf extract against amyloid-beta-induced toxicity in the Caenorhabditis elegans model of Alzheimer's disease. *Frontiers in Pharmacology*, *15*, 1408031–1408031. https://doi.org/10.3389/fphar.2024.1408031
136. Wu, M., Gao, Y., Zhang, C., Ma, B., Lin, H., Jiang, J., Xue, M., Li, S., & Wang, H. (2023a). Liensinine and neferine exert neuroprotective effects via the autophagy pathway in transgenic Caenorhabditis elegans. *BMC Complementary Medicine and Therapies*, *23*(1), 386–386. https://doi.org/10.1186/s12906-023-04183-6
137. Wu, M., Gao, Y., Zhang, C., Ma, B., Lin, H., Jiang, J., Xue, M.-F., Li, S., & Wang, H. (2023b). Liensinine and neferine exert neuroprotective effects via the autophagy pathway in transgenic Caenorhabditis elegans. In *Research Square*. https://doi.org/10.21203/rs.3.rs-3008028/v1
138. Yang, A., Bagit, A., & MacPherson, R. E. K. (2021). Resveratrol, Metabolic Dysregulation, and Alzheimer's Disease: Considerations for Neurogenerative Disease. *International Journal of Molecular Sciences*, *22*(9), 4628–4628. https://doi.org/10.3390/ijms22094628
139. You, Y. X., Shahar, S., Haron, H., & Yahya, H. M. (2018). More Ulam for Your Brain: A Review on the Potential Role of Ulam in Protecting Against Cognitive Decline. *Sains Malaysiana*, *47*(11), 2713–2729. https://doi.org/10.17576/jsm-2018-4711-15
140. Zhang, B., Wei, Y.-Z., Wang, G., Li, D., Shi, J., & Zhang, F. (2019). Targeting MAPK Pathways by Naringenin Modulates Microglia M1/M2 Polarization in Lipopolysaccharide-Stimulated Cultures. *Frontiers in Cellular Neuroscience*, *12*, 531–531. https://doi.org/10.3389/fncel.2018.00531
141. Zhang, N., Zhang, S., & Dong, X. (2024). Plant-derived bioactive compounds and their novel role in central nervous system disorder treatment via ATF4 targeting: A systematic literature review. *Biomedicine & Pharmacotherapy*, *176*, 116811–116811. https://doi.org/10.1016/j.biopha.2024.116811
142. Zhang, X., Huang, S., Xu, H., Hu, Y., & Gao, L. (2025). Research progress on plant-derived natural compounds regulating the MAPK signaling pathway for the prevention and therapy of Alzheimer's disease. *Frontiers in Pharmacology*, *16*, 1666082–1666082. https://doi.org/10.3389/fphar.2025.1666082
143. Zhao, D., Ma, L., Brownlie, J., Tonissen, K. F., Pan, Y., & Feng, Y. (2025). Neuroprotective Potential of Major Alkaloids from Nelumbo nucifera (Lotus): Mechanisms and Therapeutic Implications. *International Journal of Molecular Sciences*, *26*(17), 8280–8280. https://doi.org/10.3390/ijms26178280
144. Zhao, R. (2024). Exercise mimetics: a novel strategy to combat neuroinflammation and Alzheimer's disease. *Journal of Neuroinflammation*, *21*(1), 40–40. https://doi.org/10.1186/s12974-024-03031-9
145. Zhao, X., Shen, J., Chang, K. J., & Kim, S. H. (2014). Comparative Analysis of Antioxidant Activity and Functional Components of the Ethanol Extract of Lotus (Nelumbo nucifera) from Various Growing Regions. *Journal of Agricultural and Food Chemistry*, *62*(26), 6227–6235. https://doi.org/10.1021/jf501644t
146. Zhao, Z., Yan, J., Huang, L., & Yang, X. (2024). Phytochemicals targeting Alzheimer's disease via the AMP-activated protein kinase pathway, effects, and mechanisms of action. *Biomedicine & Pharmacotherapy*, *173*, 116373–116373. https://doi.org/10.1016/j.biopha.2024.116373
147. Zheng, Y., Zhang, X., Zhang, R., Wang, Z., Gan, J., Gao, Q., Yang, L., Xu, P., & Jiang, X. (2023). Inflammatory signaling pathways in the treatment of Alzheimer's disease with inhibitors, natural products and metabolites (Review). *International Journal of Molecular Medicine*, *52*(5). https://doi.org/10.3892/ijmm.2023.5314

148. Zhi, Y., Xie, S., & Sun, Y. (2026). Targeting aging hallmarks in brain health within the framework of preventive medicine: mechanistic insights into naringenin's role in longevity, synaptic function, and cellular homeostasis. *Frontiers in Nutrition*, *12*, 1680349–1680349. https://doi.org/10.3389/fnut.2025.1680349
149. Zhu, X., Hao, R., Lv, X., Su, J., Li, D., & Zhang, C. (2024). Neuroprotective effects of nuciferine on high-fat diet-induced cognitive dysfunction in obese mice: Role of insulin resistance, neuroinflammation, and oxidative stress. *Food Frontiers*, *5*(2), 833–844. https://doi.org/10.1002/fft2.365
150. Zhu, Z., Zhong, B., Yang, Z., Zhao, W., Shi, L., Aziz, A., Rauf, A., Aljohani, A. S. M., Alhumaydhi, F. A., & Suleria, H. A. R. (2022). LC-ESI-QTOF-MS/MS Characterization and Estimation of the Antioxidant Potential of Phenolic Compounds from Different Parts of the Lotus (Nelumbo nucifera) Seed and Rhizome. *ACS Omega*, *7*(17), 14630–14642. https://doi.org/10.1021/acsomega.1c07018