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Review article

Aluminum-induced neurotoxicity in animals: an opportunity to find effective phytochemicals for the treatment of Alzheimer's disease – a review

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Abstract

Objective: Aluminum is a non-essential neurotoxic metal. Oxidative stress, mitochondrial dysfunction, inflammation, apoptosis, alteration in the activity of acetylcholine esterase (AChE) and monoamine oxidase (MAO), β-amyloid aggregation, and tau phosphorylation have been attributed to aluminum neurotoxicity. These pathological changes bear a striking resemblance to those observed in Alzheimer's disease (AD). Therefore, animal models of aluminum neurotoxicity have been frequently used to identify effective natural products for AD treatment. This study aims to review studies that evaluate the potential therapeutic effects of plant extracts against aluminum neurotoxicity.

Materials and Methods: PubMed and ScienceDirect were searched for keywords including aluminum, neurotoxicity, plant extract, and animal models. The data extracted from each study encompassed the animal model, dose, duration, and routes of administration of aluminum and plant extracts, as well as markers of neurotransmission, oxidative stress, plaque formation, apoptosis, and inflammation.

Results: The results indicate that the healing effects of phytochemicals on aluminum-induced neurotoxicity are mediated through their metal chelating, anti-inflammatory, antioxidant, anti-apoptotic, anti-AChE, and anti-MAO activities, as well as their abilities to inhibit amyloid plaque formation.

Conclusion: Animal studies suggest that phytochemicals, either alone or in combination with anti-AD drugs, may have beneficial effects in preventing aluminum-induced neurodegeneration.

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Introduction

Aluminum is a neurotoxic element that induces histopathological and biochemical changes in the brain, resulting in deficits in learning and memory. Aluminum increases oxidative stress (OS), inflammation, acetylcholinesterase (AChE) activity, extracellular deposition of β-amyloid (Aβ),

and tau hyperphosphorylation (p-Tau) in the brain (Sanajou et al. 2023). These pathological changes bear a striking resemblance to those observed in Alzheimer's disease (AD). Given the high prevalence and associated burden of AD, many researchers have used aluminum-induced neurotoxicity in cellular and animal models to find natural products that can treat AD. SH-SY5Y cells, and PC12 cells are among the cellular models (Ghiasvand et al. 2024; Iranpak et al. 2019; Saberzadeh et al. 2016). Mice and rats are commonly used animal models that are exposed to acute (1 to 4 weeks) or chronic aluminum administration (≥ 2 months) (Drobyshev et al. 2018; Hayat et al. 2025).

Figure 1 summarizes the molecular mechanisms of aluminum neurotoxicity. Aβ plaques are derived from the abnormal processing of amyloid precursor protein (APP). Neurofibrillary tangles are formed from p-Tau. Glycogen synthase kinase-3β (GSK-3β) and protein phosphatase 2A (PP2A) are critical enzymes that regulate p-Tau levels. Consequently, the quantification of p-Tau and Aβ1-42 is a vital methodology for assessing aluminum-induced neurotoxicity (Manoharan et al. 2024). Reduced levels of acetylcholine (ACh), norepinephrine (NE), dopamine (DA), and serotonin (5-HT) have been observed in the brains of animal models treated with aluminum. The association of increased activities of monoamine oxidase (MAO) and AChE with aluminum-induced neurotoxicity has been demonstrated. Therefore, molecular docking is employed to identify phytochemicals that specifically interact with AChE and MAO (Mateev et al. 2023). The evaluation of OS involves measuring malondialdehyde (MDA), 8-oxo-guanine(8-oxo-Gua), markers of lipid and nucleic acid peroxidation, respectively, and reduced glutathione (GSH), and assay of antioxidant enzymes including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR). Increased expression of nuclear factor-E2-related factor (Nrf2) and loss of mitochondrial membrane potential (MMP) are other markers of OS (Korovesis et al. 2023). Due to the roles of apoptosis and inflammation in aluminum-induced neurotoxicity, apoptotic markers and inflammatory mediators, such as NF-κB, matrix metalloproteinases (MMPs), and interleukins, are measured to evaluate aluminum-induced neurotoxicity.

This article aims to review studies that utilized plant extracts or phytochemicals to treat aluminum-induced neurotoxicity in rodent animal models.

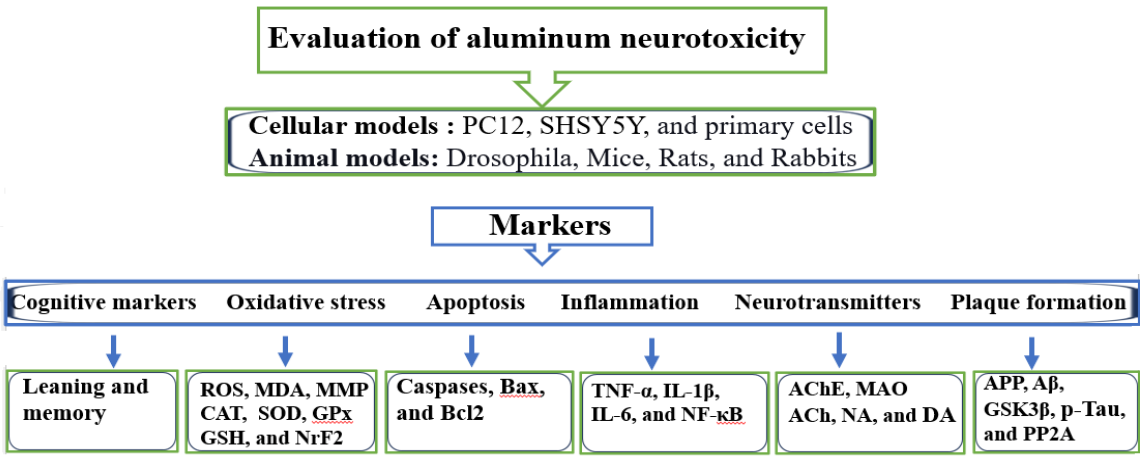

Figure 1. Cellular and animal models and markers that are applied to assess Al neurotoxicity. AChE; acetylcholinesterase, Ach; Acetylcholine, APP; amyloid precursor protein, NA; noradrenaline, DA; dopamine, MAO; monoamine oxidase, GSH; reduced glutathione, CAT; Catalase, SOD; superoxide dismutase, GPx; glutathione peroxidase, GR; glutathione reductase, MMP; matrix metalloproteinase, MDA; malondialdehyde, Aβ; β-amyloid, p-Tau; hyperphosphorylated Tau, GSK-3β; Glycogen synthase kinase-3β, PP2A; protein phosphatase 2A.

Materials and Methods

Databases such as PubMed and ScienceDirect were searched for keywords. The search strategy was: (Aluminum) AND (Neurotoxicity) AND ("Herb" OR "Plant" OR "Extract. Studies published from 2015 to August 2025 were collected Only studies with full-text articles available in English were included. Animal studies evaluating the effects of AlCl3 on behavioral, anatomical, and biochemical alterations of rats and mice were considered. Studies that used other animal models, aluminum phosphide, or exclusively investigated the effects of aluminum in *in vitro* models were excluded. The data extracted from each study included the rodent animal model, the doses of AlCl3 and phytochemicals, behavioral, biochemical, and brain structural damage results.

Results

As shown in Figure 2, phytochemicals can improve aluminum-induced neurotoxicity by targeting multiple steps, including brain aluminum accumulation, OS, AChE activity, inflammatory process, amyloid and tau aggregation, brain-derived neurotrophic factor (BDNF) expression, and tissue damage. However, these mechanisms are intricately interrelated, with their cumulative effects contributing significantly to neuronal damage and the pathological consequences associated with aluminum toxicity.

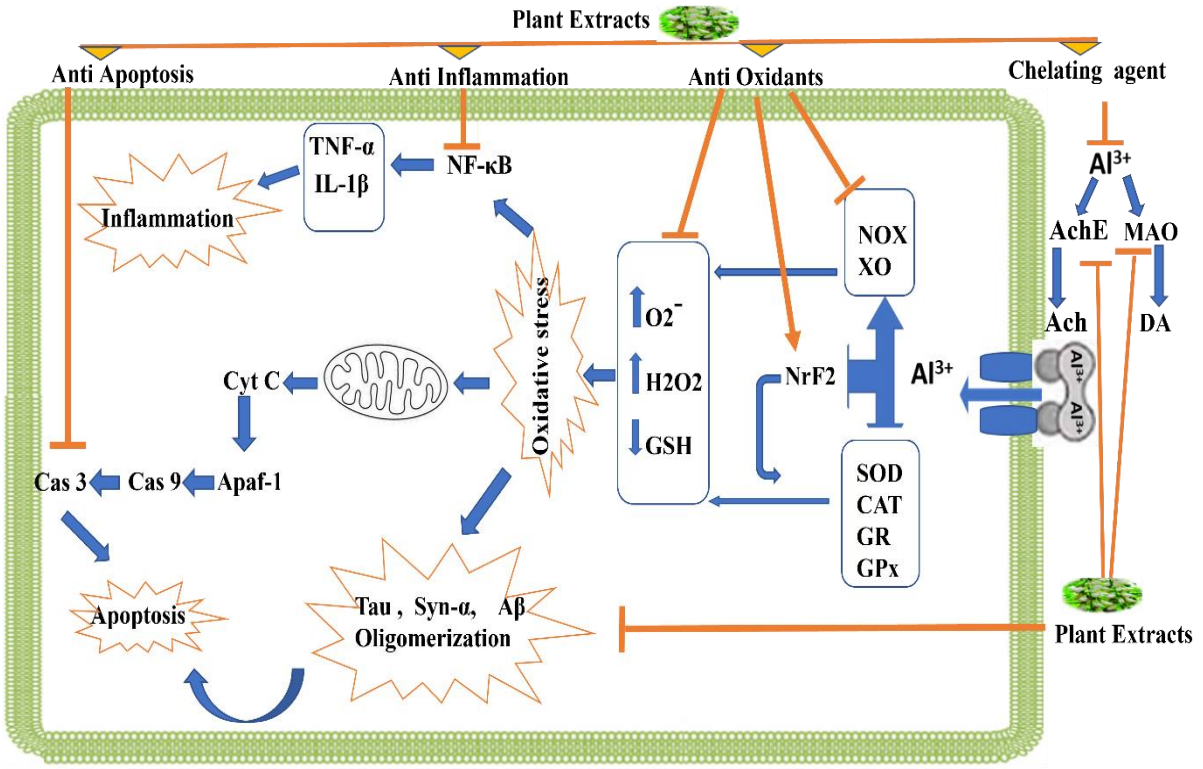

Figure 2. Aluminum-induced biochemical abnormalities within the brain may serve as potential targets for phytochemicals therapeutic interventions. AChE; acetylcholinesterase, Ach; Acetylcholine, NE; norepinephrine, DA; dopamine, MAO; monoamine oxidase, GSH; reduced glutathione, CAT; Catalase, SOD; superoxide dismutase, GPx; glutathione peroxidase, GR; glutathione reductase, Syn-α; α-Synuclein, Aβ; β-amyloid, Ach; acetylcholine, Cas3; Caspase 3, Cas9; Caspase 9,Cyt C; Cytochrome C, XO; Xanthine Oxidase, Apaf-1; Apoptotic protease activating factor 1, NOX; NADPH Oxidase, NF-kB; Nuclear factor kappa B, IL-1β; Interleukin 1 beta , Tumor necrosis factor-alpha;TNF-α.

Improving $AlCl_3$-induced behavioral impairments

Animals exposed to aluminum typically show significant deficits in learning and memory, as evidenced by longer escape latencies and reduced time spent in the target quadrant in the Morris water maze, decreased spontaneous alternation in the Y-maze, and impaired recognition and avoidance responses in the novel object recognition and passive avoidance tests. These behavioral alterations closely resemble AD-related cognitive decline(Hayat et al. 2025). All of the plant extracts included in this study (Table 1) have been shown to counteract aluminum-induced learning and memory impairments. Similarly, purified phytochemicals (Table 2) such as curcumin, resveratrol, quercetin, and chrysin exhibit strong protective effects.

A combination of several factors may be involved in this context. Given the central role of cholinergic dysfunction in AD pathology, inhibiting AChE and MAO, coupled with an increase in ACh and monoamine levels, may play a significant role. Additionally, phytochemicals may help protect against structural alterations in brain regions critical for learning and memory by mitigating OS, inflammation, and the formation of amyloid plaques. Furthermore, these compounds may enhance the expression of BDNF, supporting neuroplasticity and neuronal survival.

Reducing brain Aluminum accumulation

Aluminum can cross the blood–brain barrier (BBB) via passive diffusion as well as through transferrin-mediated transport, and accumulates in specific regions such as the hippocampus, cortex, cerebellum, and basal ganglia—areas associated with learning, memory, and motor control (Bryliński et al. 2023). Therefore, chelating agents that reduce aluminum accumulation in the brain may be useful in mitigating its neurotoxic effects (Kazmi et al. 2024). Several plant extracts and phytochemicals have been demonstrated to reduce brain aluminum accumulation and thereby attenuate its neurotoxic effects (Tables 1 and 2). Fenugreek seed extract (FSE**)** can reduce Al accumulation in the brain of aluminum-treated rats (Prema et al. 2017). Similarly, pomegranate fruit juice (PFJ) protected the AlCl3-intoxicated rats' brains by decreasing the aluminum accumulation (Gadouche et al. 2018). Among phytochemicals, curcumin and its nano-complexes have been shown to chelate aluminum via their functional β-diketone and phenolic hydroxyl groups and decrease its concentrations in the hippocampus of rats (Abdelkader et al. 2022). Quercetin is another phytochemical that reduces aluminum accumulation in the rat brain (Corrente et al. 2021).

Antioxidant effects

Oxidative stress (OS) is the central mechanism underlying aluminum-induced neurotoxicity, resulting in neuronal apoptosis, synaptic dysfunction, and cognitive impairment. Aluminum promotes OS by impairing mitochondrial electron transport, increasing labile Fe^{2+} levels that participate in Fenton reactions, suppressing key antioxidant enzymes, upregulating prooxidant enzymes such as NADPH oxidase and xanthine oxidase, and downregulating the Nrf2 pathway. Moreover, it enhances the inflammatory cascade, further amplifying oxidative damage and neuronal death, creating a vicious cycle (Abbas et al. 2022; Awad et al. 2025).

Plants are rich sources of natural antioxidants, including polyphenols, vitamin C, and vitamin E, carotenoids, terpenoids, alkaloids, and organosulfur compounds. Therefore, antioxidant effects are the most common mechanism evaluated in studies related to aluminum-induced neurotoxicity (Tables 1 and 2).

Table 1. Plant extracts with established protective effects against Aluminum-induced neurotoxicity

Treatments Dose(mg/kg/day); Duration(days)	Animal AlCl3 (mg/kg)	Major effects								Authors/year
		Memory & learning	Chelating Al3+	Antioxidant	Anti-AChE	Anti-inflammation	BDNF	Anti-apoptotic	Anti-plaque	
CAE (200- 800); (70)	WR (200)	✓						✓	✓	(Chiroma et al. 2019b) (Chiroma et al. 2019a)
CAE (150-300); (60)	WR (100)	✓		✓	✓			✓		(Firdaus et al. 2022)
BME (100,200)	WR (25)			✓				✓		(Murugan and Bhargavan 2020)
EOE (50-200); (60)	WR (100)	✓	✓		✓	✓			✓	(Justin Thenmozhi et al. 2016a)
EOE (100); (60)	WR (100)	✓		✓				✓	✓	(Justin Thenmozhi et al. 2016b)
GBE (100); (42)	SD (10) **	✓		✓	✓			✓	✓	(Verma et al. 2019)
GBE (100); (42)	SD (10) **	✓		✓	✓			✓	✓	(Verma et al. 2020)
GBE (200); (60)	Mice (20)	✓			✓	✓		✓	✓	(Abdelmeguid et al. 2021)
EJE (500) (28)	SD (17)	✓		✓	✓	✓		✓		(Hawash et al. 2023)
ROE (100); (15)	Mice (300)	✓				✓		✓		(Khalid et al. 2020)
BCSE (50) ;(14)	WR (200)	✓		✓	✓			✓		(Adelodun et al. 2021)
HSE (100); (90)	WR (50)	✓		✓	✓			✓		(Taïr et al. 2016)
ACE (60)	Mice (50)	✓		✓	✓			✓		(Singh and Goel 2015)
CA (50 - 100); (14)	WR (172.5)	✓			✓			✓	✓	(Abou Baker et al. 2020)
SOE (150); (90)	WR (60)	✓		✓	✓			✓		(Boussadia et al. 2020)
SOE (250 – 500); (20)	WR (300)	✓		✓	✓			✓		(Fatima and Tabassum 2020)
SML (10,20); (60)	SD (175)	✓		✓	✓	✓				(John et al. 2015b)
SML (1,2 mL/kg); (42)	SD (100)	✓		✓	✓	✓	✓	✓	✓	(Mohamed et al. 2021)
BT (0.75-3%) ;(60)	WR (100)	✓		✓	✓			✓	✓	(Mathiyazahan et al. 2015)
BPE (12.5)	Mice (250)	✓		✓					✓	(Iqbal et al. 2016)
FSE (5- 10%) ;(42)	WR (100)	✓		✓		✓	✓		✓	(Prema et al. 2017)
EDE (10- 300) (45)	Mice (100)	✓		✓				✓		(Thomaz et al. 2018)
HAE (100 - 200); (21)	WR (100)	✓		✓	✓	✓		✓		Anwar et al. 2021a
HSE (100); (90)	WR (100)	✓		✓	✓			✓		(Taïr et al. 2016)
PLE (150, 300) ;(60)	Mice (100)	✓		✓				✓		(Azib et al. 2019)
HPE (150, 300) ;(60)	WR (150)	✓		✓	✓	✓		✓	✓	(Cao et al. 2017a)
CCE (100, 400); (60)	WR (300)	✓		✓	✓	✓	✓	✓		(Ravi et al. 2018)
PFIE (100); (14)	SD (70)	✓		✓	✓	✓				(El-Hawary et al. 2020)
IICME (3); (15)	WR (100)	✓		✓	✓	✓		✓	✓	(Elmorsy et al. 2021)
UPE (150) (42)	WR (17)	✓		✓	✓	✓	✓	✓		(Hussein et al. 2020)
PFJ (20); (29)	Mice (40)	✓		✓				✓		(Abdulmalek et al. 2015)
PFJ (50); (90)	Mice (500)	✓	✓					✓		(Gadouche et al. 2018)
PFJ (1.47), (28)	WR (50)	✓		✓				✓		(Almuhayawi et al. 2020)
PFJ (20, 40%) ;(35)	Mice (400)	✓		✓	✓					(Abu-Taweel and Al-Mutary 2021a)
VCO (5 ml); (30)	WR (40)	✓		✓				✓		(Alghamdi 2018)
VCO (1.42 ml;(60)	WR (100)	✓		✓		✓		✓		(Khalil et al. 2020)
VCO+Betanin(5g+200 mg) ;(42)	WR (100)	✓		✓	✓	✓		✓		(Thawkar and Kaur 2024)
EPE (250) ;(56)	WR (100)	✓		✓	✓	✓		✓	✓	(Mohamed et al. 2023)
VVE (100); (21)	WR (17)	✓		✓	✓	✓	✓	✓		(Borai et al. 2017)
VVE (250, 500) (112)	WR (100)	✓		✓	✓	✓		✓	✓	(Rapaka et al. 2019)
VVE (500) (56)	WR (100)	✓		✓	✓			✓		(Aljarari and Bawazir 2019)
XPE (150,300); (60)	WR (75)	✓		✓	✓			✓		(Kemadjou Dibacto et al. 2022)
GE (50,100); (30)	WR (40)	✓		✓				✓	✓	(Li et al. 2016)
CO (100,200) ;(42)	WR (100)	✓		✓	✓					(Auti and Kulkarni 2025)
APE (200,400,600) (28)	Mice (20)	✓		✓				✓		(Ma et al. 2023)
ADE (250, 500); (6)	WR (250)	✓		✓	✓			✓		(Usman et al. 2023)
ECE (100, 300, 800); (21)	WR (300)	✓		✓	✓	✓		✓		(Saadullah et al. 2023)
GJEE (50) ()	WR (100)	✓				✓		✓		(Wang et al. 2024)
TPE (100, 200); (14)	WR(10)	✓		✓	✓			✓		(Halim et al. 2025)

Wistar rats (WR), Sprague-Dawley rat(SD), *Centella Asiatica* extract (CAE), *Bacopa Monniera* extract (BME), *Emblica Officinalis* extract (EOE*), Ginkgo Biloba* extract (GBE), *Rosemary Officinalis* extract (ROE), *Buchholzia Coriacea* seed extract (BCSE), *Hammada Scoparia* extract (HSE), *Citrus aurantium* (CA), *Salvia Officinalis* extract (SOE), *Sesamum Indicum* (SI), *Fenugreek* seed extract (FSE), *Eugenia dysenterica* extract (EDE), *Harrisonia abyssinica* extract (HAE), *Hypericum Perforatum* extract (HPE), *Caesalpinia Crista* extract (CCE), *Pistacia Lentiscus* extract (PLE), *Puntia Ficus-Indica* extract (PFIE), *Ulmus Pumila L* extract (UPE), *Eugenia Jambolana La* (EJL), *Boswellia Serrata* extract (BSE), *Indian Catechu* methanolic extract(ICME), *Pomegranate fruit* juice (PFJ), *Virgin coconut* oil (VCO), *Echinacea Purpurea* extract (EPE)**,** *Vitis vinifera* extracts (VVE), *Ginseng* extract (GE), *Premna* extracts (PE), *Camellia sinensis* (Balck Tea; BT), *Xylopia parviflora* extract (XPE), *Caraway* Oil (CO), *Salvia blancoana*, *Adansonia digitata* L. (ADE), *Thespesia populnea* L (TPE), *Euphorbia cotinifolia* (ECE),*Gardenia jasminoides J. Ellis* extract (GjEE), *Ficus lyrata* extract (FLE), *Black pepper* extract (BPE), *Allium cepa* extract (ACE),* Aluminum acetate,** Aluminum lactate

Table 2. Phytochemicals with protective effects against aluminum-induced neurotoxicity

Treatments Dose (mg/kg/day) and duration (days)	Animal (AlCl3 mg/kg)	Major effects								Authors/year
		Improved learning & memory	Chelating Al3+	Antioxidant	Anti-AChE	Anti-inflammation	BDNF	Histopathology	Anti-Aβ plaque	
Asiatic acid (75); (56)	WR (100)	✓	✓	✓	✓	✓		✓	✓	(Ahmad Rather et al. 2018)
Asiatic acid (75); (56)	WR (100)	✓		✓				✓		(Suryavanshi et al. 2022)
Curcumin (100) ;(60)	WR (75)	✓		✓	✓			✓		(Kemadjou Dibacto et al. 2022)
Curcumin (100); (90)	WR (100)	✓		✓	✓	✓		✓		(I et al. 2021)
Curcumin Essential oil (25 and 50) ;(45)	Mice (40)	✓		✓	✓			✓		(Banji et al. 2021)
Niosome Curcumin (20) ;(14)	WR (4.2)	✓				✓				(Asani et al. 2025)
Curcumin-selenium (2.5 and 25)	WR (200)	✓		✓	✓	✓		✓	✓	(Awad et al. 2025)
Curcumin+Q10 (100) ;(28)	Mice (200)	✓		✓	✓			✓		(Rasheed et al. 2025)
Genistein (10); (28)	SD (17)	✓		✓	✓	✓		✓	✓	(Wahby et al. 2017)
Quercetin (20 and 25) ;(28)	WR (50)	✓						✓	✓	(Elfiky et al. 2021)
Quercetin (20 and 25) ;(42)	WR (100)	✓	✓	✓	✓		✓	✓	✓	(Jadhav and Kulkarni 2023)
Quercetin 1, 10, and 100	Mice (10)	✓				✓		✓		(Esmaili et al. 2025)
Quercetin (25 and 50); (28)	WR (10)	✓	✓	✓	✓	✓	✓	✓	✓	(Kukolj et al. 2025)
Chrysin (10,30 and 100) ;(19)	Mice (100)	✓		✓	✓			✓		(Campos et al. 2022a)
Chrysin (1,3 and 10) (45)	Mice (100)	✓		✓	✓			✓		(Okoh et al. 2024)
Mangiferin (40); (42)	Mice (100)	✓		✓	✓	✓	✓			(Kasbe et al. 2015)
Hesperidin (50 and 100) ;(42)	Mice (100)	✓		✓	✓	✓	✓			(Jangra et al. 2015)
Hesperidin (100) ;(60)	WR (100)	✓		✓				✓		(Justin Thenmozhi et al. 2017)
Hesperidin (125 and 250); (35)	WR (172)	✓		✓	✓			✓	✓	
Silibinin (100 and 200) ;(42)	Mice (100)	✓		✓	✓	✓	✓			(Jangra et al. 2015)
Silibinin (100 and 200) ;(30)	Mice (100)	✓		✓				✓		(Makhdoomi et al. 2022)
Silymarin (200); (15)	WR (100)	✓		✓	✓	✓		✓		(Aboelwafa et al. 2020)
Silymarin (100 and 200)	WR (173)	✓	✓	✓				✓		(Li et al. 2020)
Ononin (30); (10)	SR (175)	✓		✓	✓	✓	✓	✓	✓	(Chen et al. 2021)
Resveratrol+Tannic acid (20 + 50); (90)	WR (100)	✓		✓					✓	(Bhounsule and Bhatt 2024)
Resveratrol (100) ;(9)	Mice (303)	✓				✓		✓		(Hao et al. 2021)
Thymoquinone (10,20 and 40) (14)	SD (10)	✓				✓		✓	✓	(Abulfadl et al. 2018)
Resveratrol (15 and 30); (20)	WR (10)	✓		✓	✓	✓		✓		(Benade et al. 2025)
Resveratrol (20) ;(90)	WR (100)	✓		✓		✓		✓		(Zarneshan et al. 2025)
Kaempferide (120 and 60) ;(60)	Mice (200)	✓			✓	✓				(Lin et al. 2023)
Kaempferide (5 and 10) ;(52)	WR (200)	✓		✓	✓			✓	✓	(Nalla et al. 2025)
Norbergenin (5 and 10) ;(52)	WR (200)	✓		✓	✓			✓	✓	(Nalla et al. 2025)
β-Sitosterol (50 and 100) ;(16)	WR (70)	✓		✓	✓	✓		✓		(Sajad et al. 2025)
Betalain (10 and 20) ; (28)	SD (100)	✓		✓	✓	✓		✓		(Shunan et al. 2021)
Celastrol (1) + Thymoquinone (10); (42)	WR (10)	✓		✓	✓	✓	✓	✓		(Abbas et al. 2022)
Demaghi (50 and 100) ;(28)	Mice (200)	✓		✓	✓			✓		(Ali et al. 2023)

Wistar rats (WR), Sprague-Dawley rat (SD).

Several pathways may be involved in the antioxidant effects of the phytochemicals. Some phytochemicals, such as quercetin, act as Al3+ chelators that bind to aluminum and hinder it from the reactions that lead to OS (Kukolj et al. 2025). In addition, phytochemicals can neutralize ROS by donating electrons, thereby preventing lipid peroxidation, DNA damage, and protein oxidation, which are key factors in the aluminum-induced neurotoxicity (Üremiş and Üremiş 2025). However, activating the antioxidant enzymes by the transcriptional and posttranscriptional pathways is the most common pathway that is responsible for the antioxidant effects of the phytochemicals. Resveratrol has been shown to upregulate superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) gene expression via the activation of the Nrf2 signaling pathway (Karimian et al. 2024). Similarly, quercetin increases the expression of the antioxidant enzymes by targeting Nrf2 (Jadhav and Kulkarni 2023). Genistein (Wahby et al. 2017), chrysin

(Campos et al. 2022b) and its glycosylated forms (Okoh et al. 2024), mangiferin (Kasbe et al. 2015), ononin (Chen et al. 2021), silibinin (Jangra et al. 2015), and oleracein E (Li et al. 2017) are among other phytochemicals whose abilities in inducing the activities of CAT and SOD, glutathione reductase (GR), and GPx have been demonstrated in several studies. This mechanism has also been described for the plant extracts (Table 1). *Bacopa Monniera* extract (BME) contains saponins, flavonoids, and alkaloids. Tirumanyam et al. described the role of BME and BM-silver nanoparticles in reducing OS by increasing the activities of antioxidant enzymes. (Tirumanyam et al. 2019). Similarly, *Emblica Officinalis* extract (EOE), which contains polyphenols, ascorbic acid, tannins, and gallic acid (Husain et al. 2018), can alleviate aluminum-induced OS by increasing SOD, CAT, and GPx activities (Justin Thenmozhi et al. 2016a). Adelodun et al. revealed a significant improvement in OS in the rats co-treated with *Buchholzia Coriacea* seed extract (BCSE) and $AlCl_3$. At the molecular level, BCSE increased levels of reduced glutathione (GSH) (Adelodun et al. 2021). Alkaloids are the primary constituents of the *Hammada scoparia* extract (HSE**)** (Bouaziz et al. 2016). Taır et al. demonstrated that treatment with HSE protected the animals against aluminum-induced OS by enhancing the activity of antioxidant enzymes and reducing lipid peroxidation (Taïr et al. 2016). Sesamol, an active constituent of *Sesamum Indicum* (SI) oil, enhanced CAT activity and increased GSH content in the hippocampus of AlCl3-treated animals (John et al. 2015a). Cao et al. demonstrated that *Hypericum Perforatum* extract (HPE) can increase the activity of SOD, GSH levels (Cao et al. 2017b). Ravi *et al.* demonstrated that *Caesalpinia Crista* extract (CCE) can increase CAT, GST, and GSH, and decrease MDA to normal levels in $AlCl_3$-treated rats (Ravi et al. 2018). The leaves of *Pistacia Lentiscus* extract (PLE) are rich in phenolic compounds, flavonoids, phenolic acids, and tannins. The administration of PLE reduced the adverse effects of aluminum on the activities of SOD and CAT, and neurodegeneration (Azib et al. 2019). Several studies revealed a protective effect of PFJ against aluminum-induced OS by restoring the brain CAT activity and GSH content (Almuhayawi et al. 2020) (Abu-Taweel and Al-Mutary 2021b). Khalil et al. demonstrated that Virgin coconut oil (VCO) can ameliorate aluminum-induced toxicity in rats' brains by activating the Nrf2/HO-1 signaling pathway (Khalil et al. 2020). A recent study found that curcumin-selenium nanoemulsion reduced $AlCl_3$-induced OS by increasing the expression and activities of antioxidant enzymes like CAT and SOD (Awad et al. 2025). Enhancing the activity of antioxidant enzymes through post-translational mechanisms is another mechanism described for some phytochemicals, such as Epigallocatechin gallate (EGCG) (Sun et al. 2022).

Mitochondrial dysfunction in response to aluminum exposure disrupts energy metabolism and causes OS. Several studies have shown that phytochemicals such as curcumin, quercetin, and glycyrrhizic acid supplementation effectively alleviates OS by preserving mitochondrial structure and function (Kessas et al. 2024; Rashedinia et al. 2019; Sood et al. 2011). *Centella Asiatica extract* (CAE) contains triterpenes, alkaloids, and flavonoids, including quercetin, kaempferol, catechin, rutin, and naringin (Chiroma et al. 2017). Chiroma et al. (Chiroma et al. 2019b) showed that an aqueous extract of CAE can reduce aluminum-induced cytotoxic effects by mitigating mitochondrial abnormalities. Similarly, an *in vitro* study (Rather et al. 2018) indicated that asiatic acid can reverse aluminum-induced MMP loss via regulating the AKT/GSK-3β pathway.

Finally, many phytochemicals, such as curcumin and resveratrol, exhibit anti-inflammatory properties by downregulating

pro-inflammatory pathways such as NF-κB and MAPK. Inflammation can lead to OS by triggering the production of ROS. The detailed mechanisms underlying these anti-inflammatory effects will be discussed in the subsequent section.

Anti-inflammatory effects

Aluminum is strongly linked to neuroinflammation by several mechanisms. Aluminum activates microglia, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6 (Abbas et al. 2022; Saadullah et al. 2023). Moreover, it induces the generation of reactive oxygen species (ROS), which activates the NF-κB signaling pathway(Lin et al. 2023). Aluminum can also activate the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, which leads to the maturation and secretion of pro-inflammatory cytokines like IL-1β (Thawkar and Kaur 2024). Additionally, aluminum compromises the integrity of the BBB, allowing immune cells to infiltrate the brain and further promote inflammation. In addition to these effects, aluminum promotes Aβ aggregation and fosters a chronic inflammatory environment. Lastly, aluminum exposure disrupts the balance of neurotransmitters such as acetylcholine and glutamate, further enhancing excitotoxicity and inflammation in the brain (Lin et al. 2023).

Anti-inflammatory effects of many phytochemicals have been demonstrated (Tables 1and 2). EOE (Dhivya Bharathi et al. 2019), *harrisonia abyssinica extract* (HAE) (Anwar et al. 2021), HPE (Cao et al. 2017b), and CCE (Ravi et al. 2018) are amongst plant extracts that showed anti-inflammatory effects and reduced the expression of IL-1b, IL-6, and TNF-α in the hippocampus of $AlCl_3$-exposed rats. Curcumin (Awad et al. 2025), quercetin (Kukolj et al. 2025), resveratrol (Benade et al. 2025), and silymarin (Aboelwafa et al. 2020) are phytochemicals with anti-inflammatory effects (Table 2).

Several possible mechanisms may be responsible for the anti-inflammatory effects of phytochemicals. One key mechanism is through their ability to scavenge ROS. Many phytochemicals are potent antioxidants that ameliorate aluminum-induced neuroinflammation by neutralizing ROS and preventing the activation of NF-κB and mitogen-activated protein kinases (MAPKs). Decreasing the levels of Aβ, which is known for its inflammatory effects, is another mechanism. It has been found that curcumin-selenium nanoemulsion reduced $AlCl_3$-induced brain damage by decreasing the levels of Aβ, TNF-α, and nitric oxide (Awad et al. 2025). Additionally, phytochemicals can modulate microglial activation, a central process in neuroinflammation. For example, quercetin and kaempferol, found in a variety of fruits and vegetables, have been shown to inhibit TLR4 signaling in microglia, reducing the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. The combination of phytochemicals such as betanin and virgin coconut oil has been shown to influence the NLR, reducing the production of IL-1β and mitigating inflammation-induced neuronal damage (Thawkar and Kaur 2024). Lastly, phytochemicals may promote the restoration of blood-brain barrier integrity, which is often compromised during aluminum toxicity, thus protecting the brain from excessive immune cell infiltration and reducing the overall inflammatory burden (Tkaczenko et al. 2025).

Targeting AChE Activity

Cholinergic dysfunction, characterized by an elevated brain AChE activity and reduced ACh levels, is a common hallmark of AD and aluminum toxicity (Farhat et al. 2017). Aluminum increases AChE activity by direct and indirect mechanisms, including the induction of conformational changes and the modulation of AChE gene expression. AChE plays a dual role in the pathogenesis of Aluminum neurotoxicity

and AD pathogenesis. AChE increases acetylcholine turnover. Furthermore, it promotes Aβ aggregation by forming the AChE–Aβ complex, enhancing neurotoxicity. AChE inhibitors are being explored as potential therapies for AD and for mitigating aluminum-induced neurotoxicity (Grabowska et al. 2025).

Experimental and molecular docking studies suggest that phytochemicals can target and inhibit AChE via direct inhibition or reducing its expression. Phytochemicals such as curcumin, rosmarinic acid, quercetin, silibinin, chrysin, ononin, and silymarin have demonstrated significant AChE inhibitory activity, exhibiting varying IC_{50} values depending on their chemical structures and experimental conditions (Gajendra et al. 2024). Similarly, the effects of various plant extracts in mitigating aluminum-induced AChE activity have been demonstrated in several studies (Table 1). Several plant extracts have progressed to clinical trials, and some of them have even received FDA approval for their AChE inhibitory properties (Gajendra et al. 2024). However, some points are necessary to be considered. First, the type of extraction can greatly influence the AChE inhibitory potential of plant extracts, as different solvents selectively extract specific bioactive compounds. (Ihsan et al. 2022). Second, other factors such as phytochemical composition, plant part used, plant maturity, geographical origin, extraction conditions, and storage or processing methods can also affect the potency of plant extracts, emphasizing the complexity of optimizing natural products for neuroprotective applications (Sun et al. 2025). Phytochemicals can also modulate the expression of AChE in the brain. For example, a strong inhibition of AChE mRNA transcription in the frontal cortex of rats treated with *Salvia miltiorrhiza* was observed in both the frontal cortex and hippocampus (Ozarowski et al. 2017).

Anti-amyloid and Tau-modulating effects

Aluminum neurotoxicity has been linked to deposition of Aβ plaques and p-Tau, key features of AD. Studies have demonstrated that aluminum increases the expression of APP. Moreover, the normal processing of APP via α-secretase is inhibited, while the abnormal pathway facilitated by β-secretase is augmented by aluminum (Abulfadl et al. 2018). In terms of p-Tau, Aluminum activates kinases such as GSK-3β, leading to tau aggregation into neurofibrillary tangles. Additionally, aluminum inhibits PP2A, preventing tau dephosphorylation (Chiroma et al. 2019a).

Phytochemicals can reverse aluminum-induced amyloidogenesis and p-Tau through their abilities in decreasing OS, inflammation, and regulating the pathways involved in deposition of Aβ plaques and p-Tau. Several plant extracts (Table 1) and phytochemicals (Table 2) improve OS and prevent the activation of key inflammatory pathways like NF-κB and MAPKs, which are critical in both Aβ aggregation and p-Tau. Thymoquinone has been demonstrated to inhibit the release of pro-inflammatory cytokines like TNF-α and IL-1β that activate tau kinases such as GSK-3β (Abulfadl et al. 2018). Polyphenols also reduce p-Tau by inhibiting GSK-3β activity, increasing PP2A activity, and enhancing p-Tau clearance (Zheng et al. 2019).

Moreover, studies have demonstrated that certain phytochemicals can augment α-secretase and inhibit β-secretase. For example, quercetin has been shown to reduce Aβ plaque formation by upregulating the expression of α-secretase, leading to inhibition of Aβ production (Elfiky et al. 2021). Ginseng protein has been found to reduce Aβ1-42 and p-tau through modulating PI3K/Akt signaling pathway (Li et al. 2016). Moreover, many phytochemicals have metal-chelating properties that bind and neutralize Al^{3+}, preventing their accumulation in the brain (Tables 1 and 2). In addition, polyphenols

can attach to the Aβ42-metal ion complex and dissociate metal ions from Aβ42, which decreases the toxicity of the Aβ42-metal complex (Lakey-Beitia et al. 2021). By restoring normal metal homeostasis, these compounds prevent the disruption of amyloid-beta metabolism and reduce the toxic accumulation of Aβ plaques and tau tangles.

Phytochemicals can also enhance the clearance of Aβ by facilitating the disaggregation of fibrillar structures. Molecular models indicate that curcumin and quercetin prevent Aβ42 oligomerization by stabilizing the stabilization of monomeric form of Aβ. Resveratrol has been shown to enhance the clearance of Aβ monomers, whereas rosmarinic acid and curcumin directly inhibit oligomerization by disrupting peptide interactions. Furthermore, resveratrol can restructure harmful Aβ oligomers into non-toxic forms (Lakey-Beitia et al. 2021).

BDNF expression

Brain-derived neurotrophic factor (BDNF) is a key neurotrophic factor that supports neuronal survival, synaptic plasticity, and cognitive functions, including learning and memory. In AD, BDNF expression is significantly reduced, contributing to the degeneration of neurons, particularly in the hippocampus. The loss of BDNF impairs synaptic plasticity and accelerates neurodegeneration (Gao et al. 2022). Studies have demonstrated that aluminum can decrease brain BDNF levels (Jadhav and Kulkarni 2023). Therefore, research has focused on restoring BDNF expression as a potential therapeutic approach for AD and aluminum-induced neurotoxicity. Phytochemicals have demonstrated the ability to upregulate BDNF expression. Silibinin increased BDNF content in the hippocampus of $AlCl_3$-treated animals (Jangra et al. 2015). Mangiferin is another phenolic compound that can prevent hippocampal BDNF depletion induced by $AlCl_3$ (Kasbe et al. 2015). Chen et al. revealed that BDNF and PPAR-γ increased following treatment with ononin (Chen et al. 2021). Recently, the protective effects of quercetin against aluminum-induced brain toxicity have been evaluated and it was found that quercetin improved memory function, reduced and increased BDNF in aluminum-treated animals (Kukolj et al. 2025). In a recent study, aluminum caused memory impairment and reduced hippocampal BDNF and p-Akt levels in mice, while curcumin prevented memory loss and mildly restored BDNF and p-Akt, suggesting its neuroprotective role may involve BDNF and Akt signaling (Reiszadeh Jahromi et al. 2025). Although the exact molecular mechanisms were not fully determined, it has been suggested that phytochemicals can enhance BDNF expression through several key signaling pathways, including PI3K/Akt, MAPK/ERK, and SIRT1 (Singh et al. 2025).

Anti-apoptotic effects

Apoptosis is a common feature of AD and aluminum-induced neurotoxicity. Aluminum was shown to induce apoptosis in neurons through both intrinsic and extrinsic pathways (Prema et al. 2016). The intrinsic pathway is directly related to aluminum-induced mitochondrial dysfunction and Bax-mediated cytochrome c release. Aluminum was shown to increase the rate of cytochrome c binding to Apaf1 with subsequent activation of caspase 9 and caspase 3, promoting apoptosis. Another pathway of aluminum proapoptotic effect involves Fas/FasL signaling, with activation of caspase 3 following caspase 8 stimulation (Skalny et al. 2021).

Phytochemicals exert powerful neuroprotective effects against AlCl3-induced apoptosis, through several mechanisms (Tables 1 and 2). As previously described, many phytochemicals enhance endogenous antioxidant defenses by upregulating antioxidant enzymes, thereby reducing OS

and preserving mitochondrial integrity; for example, quercetin and resveratrol are known to elevate SOD and GPx levels in neuronal tissues (Chiroma et al. 2019b). Similarly, asiatic acid can reverse Aluminum-induced MMP loss via regulating the AKT/GSK-3β pathway (Rather et al. 2018).

Phytochemicals also regulate apoptosis by upregulating the anti-apoptotic Bcl-2 and downregulating the pro-apoptotic Bax, thereby preventing the release of cytochrome c and the activation of caspase cascades (Kar et al. 2019; Sharma et al. 2016). Oleracein E increased Bcl-2 and reduced Bax expression in the CA4 and CA1 regions of the brain, suggesting its anti-apoptotic effects (Li et al. 2017). Anwar et al. demonstrated that HAE can normalize the adverse effects of aluminum on Bcl2 expression (Anwar et al. 2021). Some phytochemicals also downregulate p53 expression, a key mediator of DNA damage-induced apoptosis, and reduce mitochondrial-mediated cell death (Cao et al. 2019; Sharma et al. 2016). In addition, several phenolic compounds inhibit microglial activation and the release of pro-inflammatory cytokines such as TNF-α and IL-1β, which are known to activate death receptors like Fas and tumor necrosis factor receptor (TNFR) (Kessas et al. 2024; Sedik et al. 2025). Lastly, many phytochemicals, including curcumin and Eugenol, inhibit the NF-κB signaling pathway, thereby blocking the transcription of genes involved in inflammation and apoptosis (Kumar et al. 2025; Prakash et al. 2025).

Discussion

This review provides compelling evidence that plant extracts and phytochemicals exert protective effects against aluminum-induced neurotoxicity. The inclusion of cognitive impairment, a major symptom and a significant health risk associated with aluminum and AD (Halim et al. 2025), alongside biochemical and histological evaluations offer functionally relevant evidence of neuroprotection, as improved learning and memory performance directly reflect the restoration of neuronal integrity and neurotransmission. Furthermore, phytochemicals were shown to target various aspects of aluminum-induced neurotoxicity, including aluminum accumulation, OS, neuroinflammation, neuronal damage, Aβ accumulation, p-Tau, and AChE hyperactivity. These mechanisms are also central to AD pathology, suggesting that phytochemicals may exert multifaceted neuroprotective effects through both antioxidant and anti-inflammatory pathways. In most of the reviewed studies, phytochemicals demonstrated therapeutic effects comparable to those of rivastigmine and donepezil, standard AChE inhibitors used in AD therapy (Bhounsule and Bhatt 2024). This highlights their potential as natural therapeutic agents for ameliorating cognitive impairments in AD patients. Among the reviewed plant extracts, GBE, VVE, quercetin, curcumin, and resveratrol were the most consistently effective against aluminum-induced neurotoxicity. Their neuroprotective effects arise mainly from antioxidant, anti-inflammatory, and anti-AChE activities that improve cognition and reduce neuronal damage. Reported inconsistencies likely stem from variations in dosage, treatment duration, experimental models, and extract standardization. Nonetheless, these extracts show strong multifunctional potential, warranting standardized studies to confirm efficacy and translational relevance.

Another strength of the reviewed studies is the inclusion of both acute and chronic aluminum exposure models. Chronic exposure models are particularly valuable because they more closely approximate the progressive neurodegeneration observed in AD, while acute exposure models reveal short-term protective mechanisms. Together, these findings suggest that phytochemicals may exert both immediate and sustained

neuroprotective effects, depending on the duration and severity of neurotoxic insult.

Most of the plant extracts reviewed demonstrated the ability to modulate the activities of AChE and MAO—two critical enzymes implicated in AD pathogenesis. Drugs with dual inhibitory effects against AChE and MAO have been reported to possess superior efficacy compared to agents targeting either enzyme alone. Therefore, identifying phytochemicals with dual inhibitory properties may represent a promising direction for developing more effective therapeutic strategies against AD (Asim et al. 2025).

Despite these promising results, several limitations should be noted. One limitation arises from the heterogeneity of experimental protocols. The mode of aluminum exposure varied substantially among studies, including differences in concentration, duration (acute versus chronic exposure), and, in some cases, co-administration with D-galactose. The inclusion of D-galactose, commonly used to mimic aging-related oxidative stress (Pantiya et al. 2023), may confound the interpretation of Aluminum-specific effects and phytochemical efficacy. Thus, standardization of aluminum exposure models is necessary to improve the reproducibility and comparability of results.

Additionally, there is a limitation regarding the scope of pathological assessment. Although a few studies comprehensively evaluated multiple AD-like hallmarks—such as Aβ deposition, p-Tau, OS, and neuroinflammation—most studies focused predominantly on antioxidant activity. Given the multifactorial nature of AD, more integrative studies are needed to elucidate the interactions between OS, inflammation, and protein aggregation under phytochemical treatment. Furthermore, systemic toxicity assessments were rarely included. Most studies employing plant extracts did not evaluate potential hepatic or renal toxicity, despite the crucial role of these organs in metabolizing phytochemicals. Without comprehensive toxicological data, conclusions regarding the long-term safety and therapeutic applicability of these compounds remain tentative.

The heterogeneity in the quality of botanical products, due to factors such as genetic variation, agricultural practices, and post-harvest processing, can affect consistency and efficacy. Additionally, many phytochemicals suffer from poor aqueous solubility, instability, rapid metabolic degradation, and limited permeability across the BBB. While polyphenols and polysaccharides exhibit low BBB permeability, the lipophilic nature of alkaloids and carotenoids also restricts their bioavailability. Glycosylation has emerged as a simpler and more cost-effective approach to improve stability and solubility. For example, glycosylated chrysin demonstrates superior antioxidant and neuroprotective effects compared to its aglycone form (Okoh et al. 2024). These strategies represent promising directions for enhancing the pharmacological potential of phytochemicals.

Beyond these experimental factors, the clinical translation of phytochemicals faces substantial challenges. While aluminum-induced neurotoxicity is frequently used to study AD and mimics several aspects of AD pathology, it does not fully replicate the complex and multifactorial nature of AD. AD is influenced by an intricate interplay of genetic, metabolic, and environmental factors, including amyloid plaques, tau tangles, cholinergic dysfunction, and vascular impairment. As such, aluminum-induced neurotoxicity represents a simplified model that may not accurately represent the genetic or molecular mechanisms underlying amyloid-β and tau pathology in humans. Therefore, while useful for preliminary screening of neuroprotective agents, $AlCl_3$ models should be interpreted cautiously when extrapolating findings to clinical contexts. Moreover, this limitation suggests that

while phytochemicals may offer protective effects in aluminum-exposed animals, their efficacy in the broader, more complex landscape of AD should be approached with caution.

One limitation of this review is the absence of a formal risk of bias assessment for the included animal studies. The use of structured tools, such as SYRCLE's Risk of Bias tool, would provide a more systematic evaluation of study quality and internal validity, thereby increasing the rigor and reliability of future reviews in this field.

In summary, phytochemicals show considerable promise as neuroprotective agents against Aluminum-induced neurotoxicity through their antioxidant, anti-inflammatory, anti-AChE, and anti-apoptotic properties. However, substantial heterogeneity among studies, limited systemic toxicity assessments, and persistent challenges related to bioavailability, pharmacokinetics, and extract standardization underscore the need for more rigorous experimental and translational research. Despite these obstacles, compounds such as curcumin, resveratrol, and GBE demonstrate encouraging translational potential, supported by favorable safety profiles and preliminary clinical evidence of cognitive benefit. Future investigations should emphasize standardized aluminum exposure protocols, comprehensive evaluation of AD-like pathology, exploration of combination and dual-inhibitor therapies, and the application of advanced formulation and delivery techniques to enhance bioavailability and facilitate clinical validation.

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Conflicts of interest

The authors had no competing interests.

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Ethical Considerations:

This review synthesizes existing published literature. As no new data was collected or human participants directly involved, ethical approval was not required. All sources are properly cited, adhering to academic integrity.

Authors' Contributions

Study design: F.I, M.K, R.A, J.S, M.A.T; Supervision: M.A.T; Visualization: F.I, M.K, M.A.T; Investigation: F.I, M.K, R.A, J.S, M.A.T; Draft manuscript preparation: F.I, M.K, R.A, J.S, M.A.T; Critical revision : M.K, M.A.T. All the authors reviewed and approved the final version of the manuscript.

Abbreviations:

Aβ; β-amyloid,AD: Alzheimer's disease,Apaf-1; Apoptotic protease activating factor 1, APP; Amyloid precursor protein, Ach; Acetylcholine AChE; Acetylcholinesterase, BBB; Blood brain barrier, BDNF: Brain-derived neurotrophic factor , CAT; Catalase, Cas3; Caspase 3, Cas9; Caspase 9, Cyt C; Cytochrome C, DA; Dopamine, GSK-3β; Glycogen synthase kinase-3β, GSH; Reduced glutathione, GPx; Glutathione peroxidase, GR; Glutathione reductase, IL-1β; Interleukin 1 beta , MAO; Monoamine oxidase, MMP; Matrix metalloproteinase, MDA; Malondialdehyde, NA; Noradrenaline, NE; Norepinephrine, NLRP3: NLR family pyrin domain-containing 3, NOX; NADPH Oxidase, NF-kB; Nuclear factor kappa B, OS: Oxidative stress, PP2A; protein phosphatase 2A, p-Tau; hyperphosphorylated Tau, ROS: Reactive oxygen species ,SOD; Superoxide dismutase, Syn-α; α-Synuclein, TNF-α: Tumor necrosis factor-alpha, TNFR: Tumor necrosis factor receptor, XO; Xanthine Oxidase

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