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The Neuroprotective and Therapeutic Effects of Medicinal Plants and Natural Products against Aluminium Chloride-Induced Alzheimer's Disease: Recent Update

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Abstract

Alzheimer's disease currently affects more than 35 million individuals worldwide. Aluminium has been implicated in the pathogenesis of various cognitive disorders. Meanwhile, aluminium chloride ($AlCl_3$) has a significant impact on the progression of neurodegenerative diseases including Alzheimer's disease. The majority of Alzheimer's disease medications now on the market are cholinesterase inhibitors. However, the effectiveness of these drugs is limited because they can't totally arrest the progression of the disease. The utilization of medicinal plants and natural products may present excellent prospective options for Alzheimer's disease prevention and therapy. This study summarized medicinal plants and natural products for the prevention and treatment of $AlCl_3$-induced Alzheimer's disease as an alternative therapy using published data in the literature from the years 2021-2023. The medicinal plants and natural products help to reduce Alzheimer's disease pathogenesis by controlling different pathways and could be used as a therapeutic agent against the symptoms. The majority of the medicinal plants and natural products discussed in this review have been shown to have neuroprotective, antioxidant, anti-amyloid, anti-inflammatory, anticholinesterase, anti-apoptotic, and therapeutic actions. Therefore, medicinal plants and natural products may offer neuroprotective and therapeutic effects in the treatment of Alzheimer's disease.

Keywords: Aluminium chloride; Alzheimer's disease; Complementary and alternative medicine; Medicinal plants; Natural products.

Abbreviations: ACh: Acetylcholine; AChE: Acetylcholinesterase; AD: Alzheimer's disease; Al: Aluminium; $AlCl_3$: Aluminium Chloride; APP: Amyloid precursor protein; Aβ: Amyloid-beta; b.wt.: body weight; BACE1: β-amyloid converting enzyme 1; BBB: Blood–brain barrier; BChE: Butyrylcholinesterase; BDNF: Brain-derived neurotrophic factor; CAT: Catalase; COX-2: Cyclooxygenase-2; ERK1/2: extracellular regulated kinase; GPx: Glutathione peroxidase; GSH: Glutathione; i.p.: intraperitoneally; IL-1α: Interleukin-1 alpha; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; MDA: Malondialdehyde; NDs: Neurodegenerative diseases; NFT: Neurofibrillary tangles; NF-κB: Nuclear factor-kappa B; NMDA: N-methyl D-aspartate; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor 2; p.o.: Oral administration; PON-1: Paraoxonase 1; ROS: Reactive oxygen species; s.c.: subcutaneous; SOD: Superoxide dismutase; TAC: Total antioxidant capacity; TBARS: Thiobarbituric acid-reactive substances; TNF-α: Tumor necrosis factor-alpha; TNF-β: Tumor necrosis factor-beta

INTRODUCTION

The most prevalent form of dementia, Alzheimer's disease (AD), currently affects more than 35 million individuals worldwide. This number is estimated to rise to 65 million by 2030 and 115 million by 2050 (Ricci 2019). As the fifth most common cause of death in the elderly population, AD may make patients more susceptible to accidents via dementia and cognitive deterioration (Yang et al. 2020). As the percentage of the population that is 65 years of age or older increases steeply, it is anticipated that the number of people with AD will significantly increase in the coming years (Shunan et al. 2021). Although the pathophysiology of AD is unknown, neuritic plaques, neurofibrillary tangles (NFT), and the loss of cholinergic neurons in the nucleus basalis of Meynert are the main features of AD neuropathology. Its pathogenesis has been attributed to a variety of etiological factors. Some risk genes may promote the deposition of amyloid beta (Aβ) plaques and aberrant tau protein phosphorylation**,** which results in the formation of common NFTs (Kunkle et al. 2019). Additionally, oxidative stress, inflammation, hormonal deficiency (estrogen), and aging altogether have a corroborative role (Kong et al. 2019; Selkoe 2019; Simunkova et al. 2019).

A common neurotoxin like aluminium (Al) has been implicated in the pathogenesis of various cognitive disorders (Lukiw et al. 2019). Chronic exposure to Al has also been implicated in the appearance of neurologic signs like progressive neurodegeneration, changes in the

neuro-filament of the hippocampus and cerebral cortex, and other biochemical changes of clinical importance. Aluminium chloride ($AlCl_3$) has a significant impact on the progression of neurodegenerative diseases including AD and Parkinson's disease (Efosa et al. 2023). The majority of the metals found in the crust of the Earth are aluminium. Everything we eat, drink, breathe, and consume contains it, including water, food, beverages, flavoured drinks, energy drinks, medicine, dust, and air (Abd El-Aziz et al. 2023). The ability of aluminum to cross the blood-brain barrier (BBB) and accumulate in the brain results from its incredibly high affinity to transferrin receptors (Nie 2018). Both *in vivo* and *in vitro*, this metal causes neuronal death. Aluminum may actively be involved in the genesis of major neuropathologic lesions in Alzheimer's disease and other illnesses by cross-linking hyperphosphorylated proteins (Abd El-Aziz et al. 2023).

The majority of AD medications now on the market are cholinesterase inhibitors. However, the effectiveness of these drugs is limited because they can not totally arrest the disease's progression (Sharma 2019). This might be caused by the complex nature of the disease etiology. Also, up to date, all available treatments exhibit adverse side effects which could aggravate to stroke and death (Liu et al. 2018). As a result, a drug that has both anticholinesterase properties and many protective activities may be a viable treatment for AD. Numerous plants have been found to be therapeutically effective in cases of memory loss, AD, and disorders associated with ageing. Phenolic-rich medicinal plants have recently attracted a lot of attention as potential treatments for neurodegenerative diseases (NDs) like AD due to their powerful anti-inflammatory and antioxidant properties (Freyssin et al. 2020). In recent years, natural products derived from plants and their bioactive components have been extensively studied for their therapeutic potential in a variety of neurodegenerative diseases (NDs), including AD. Although there have been remarkable advances in our understanding of NDs, there has not been much success in developing effective treatments. The utilization of natural products may present excellent prospective options for NDs prevention and therapy (Rahman et al. 2021).

A study (Pandey et al. 2021) summarized frequently used medicinal plants and herbs and their phytochemical components for the treatment and diagnosis of Alzheimer's disease as an alternative therapy. However, this study presents an updated summary of medicinal plants and natural products with potential therapeutic and preventive properties against Aluminium chloride-induced Alzheimer's disease. Moreover, combining pharmacological therapy with herbal and natural remedies that support various processes and goals may be an effective way to treat and control AD. The studies mentioned in this study demonstrated that natural products may slow the onset of disease. It would be very advantageous to use the knowledge gained from this study to help develop ethnomedicinal drugs that work with AD therapies.

METHODOLOGY

This paper used information from existing peer-reviewed journals to conduct a literature review. The following databases were used in the literature search: PubMed, Google Scholar, ScienceDirect, Embase, Scopus, and Web of Science. Articles that used animal models, evaluated medicinal/herbal plants and/or natural products from plants used against aluminium chloride ($AlCl_3$)-induced Alzheimer's disease, and were published in English between 2021 and 2023 met the inclusion criteria. The exclusion criteria were review articles, clinical trials, conference papers, research conducted *in vitro*, studies older than 2021, and studies that administered or co-administered other toxicants (such as scopolamine, D-galactose, iron, or streptozotocin) to induce Alzheimer's disease.

MECHANISM OF ALUMINIUM CHLORIDE-INDUCED ALZHEIMER'S DISEASE

Aluminum (Al) promotes the genesis of several neurodegenerative diseases by affecting a number of neurotoxic biomolecules (Abbas et al. 2022; Mehrbeheshti et al. 2022). Al is known to accelerate oxidative stress, the formation of plaques, and the cross-linking & deposition of Aβ oligomers in the brain cortex and hippocampus. Thus, the neuroprotective effects of numerous phytochemicals and chemical compounds against AD can therefore be studied using $AlCl_3$-induced AD in rats as a suitable model (Elbini-Dhouib et al. 2021; Aalikhani et al. 2022; Chen et al. 2022). Al exposure is essentially inevitable due to its prevalence in the environment, everyday activities, and food (Mesole et al. 2020; Skalny et al. 2021).

The hallmark of AD is the accumulation of Aβ plaques and NFTs in the brain. Aβ production is initiated by the cleavage of amyloid precursor protein (APP) by β-secretase, which is commonly known as beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), and ɣ-secretase enzymes (Islam et al. 2022). Aβ can easily diffuse across the brain parenchyma and trigger a cascade of pathogenic processes such as neuronal apoptosis/necrosis, development of oxidative stress, and neuroinflammation in the cortex and hippocampus (Morroni et al. 2018). Al-maltolate exposure was demonstrated to increase Aβ1–42 expression via up-regulating APP, β-(BACE1), & γ-secretase (presenilin-1) mRNA transcription and protein expression in rat brain regions (Liang et al. 2013; Thenmozhi et al. 2015). These changes also correspond to a significant decrease of α-secretase proteins (Wang et al. 2014).

Evidence suggests that, in addition to amyloid proteins and tau, these protein aggregates may stimulate the immune system for a long period of time and cause the release of chemokines, proinflammatory cytokines, and neurotoxins like reactive oxygen species (ROS), nitric oxide (NO), and excitatory amino acids, which can further damage and degenerate neurons (Calsolaro and Edison 2016; Zhang et al. 2017). However, a rising body of evidence points to free radical damage to the brain's lipid, protein, carbohydrate, and DNA as the cause of neuronal death (Padurariu et al. 2013). Alzheimer's disease brains exhibit excessive ROS generation and impaired antioxidant to oxidative stress (Zhao and Zhao 2013).

Alzheimer's disease has also been linked to mitochondrial dysfunction, increased permeability, excessive ROS production, and impaired mitochondrial membrane capacity. Superoxide anion, hydroxyl radical, hydrogen peroxide, and nitric oxide have all been implicated in oxidative stress-mediated neurodegeneration in Alzheimer's disease (Pandey et al. 2021).

Numerous deleterious effects of Al, including neurotoxicity, are caused by oxidative stress and mitochondrial dysfunction (Kumar and Gill 2014). a significant decrease in the activity of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase, and glutathione-S-transferase (GST) was linked to the observed increase in brain lipid peroxidation under Al exposure. Al exposure was also demonstrated to lower Mn-SOD activity in the mitochondria, which contributed to the development of mitochondrial dysfunction (Skalny et al. 2021).

The interference of Al with neurotransmitter metabolism and signal transduction is at least largely responsible for the negative neurological effects of exposure to Al. furthermore, the available results unambiguously show that Al exposure significantly affects glutamatergic, cholinergic, gabaergic, dopaminergic, and serotoninergic neurotransmission even though the exact mechanisms are yet unknown (Skalny et al. 2021). According to several studies, Al increased the activity of the enzyme acetylcholinesterase (AChE) in the brain (Khan et al. 2013). Aluminum is a powerful cholinotoxin which enhanced AChE activities by modifying the secondary structure of the enzyme, which significantly impede the cholinergic transmission in the brain (Kakkar and Kaur 2011). As its dysfunctions are mostly associated with the severity of dementia in AD patients, cholinergic transmission has a high priority in the pathogenesis of AD (Thakur et al. 2019). Al administration also led to an elevated level of glutamate alpha-decarboxylase activity as well as a significant increase in glutamate levels in the hippocampus, thalamus, and cerebellum (Skalny et al. 2021). Aluminum exposure causes glutamate increase, which causes excitotoxic damage, degeneration, and death in neurons. Glutamate impairs learning and memory by overstimulating of N-methyl D-aspartate (NMDA) receptors and causing cognitive decline and neuronal death (Alghamdi et al. 2018). Generally, $AlCl_3$ neurotoxicity has been shown to result in mitochondrial dysfunction, oxidative and endoplasmic reticulum stress, inflammation, cell death, interaction with Aβ and α-synuclein, cytoskeletal abnormalities, and alteration of synaptic plasticity and signal transduction through interference with neurotransmitter systems (Skalny et al. 2021).

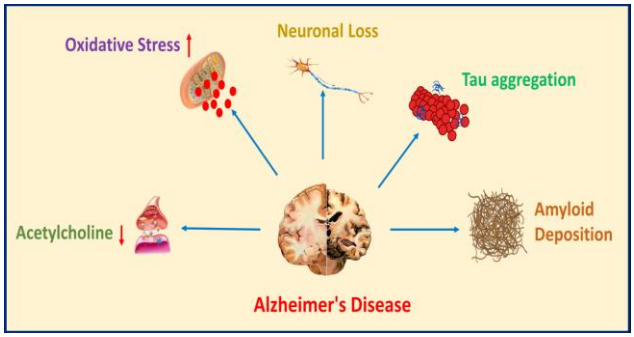

Figure 1. Mechanism of Aluminium chloride-induced Alzheimer's disease (Dabhekar et al. 2022).

ROLE OF MEDICINAL PLANTS AGAINST ALUMINIUM CHLORIDE-INDUCED ALZHEIMER'S DISEASE

Acacia catechu

Acacia catechu, commonly referred to as "khair" in India, has been suggested as a viable treatment for AD due to its powerful anticholinesterase and antioxidant properties. *A. catechu* methanolic extract significantly enhanced cholinergic neurotransmission in rats, decreased the genotoxic effects of $AlCl_3$, and significantly improved histopathological and biochemical findings (Elmorsy et al. 2021).

Hibiscus sabdariffa

In phytomedicine, the use of fresh calyx of the therapeutic herb *Hibiscus sabdariffa* is gaining popularity. In a study, $AlCl_3$ significantly increased malondialdehyde (MDA), and decreased glutathione (GSH), GPx, SOD, and CAT activities significantly in the brain of experimental rats, but these effects were significantly reversed by treatment with *H. sabdariffa*. Also, $AlCl_3$ significantly lowered protein levels and increased percentage inhibition of AChE and butyrylcholinesterase (BChE) activities in the brain of test rats, however, treatment with *H. sabdariffa*, at low and high doses significantly reversed these effects (Efosa et al. 2023). Similarly, *H. sabdariffa* synthesized-gold nanoparticles (HS-AuNPs) ameliorated AD-related memory and learning impairments. HS-AuNPs also

ameliorated the reduction in SOD, GPx, and GSH activities, and ameliorated the elevation of AChE, monoamine oxidase (MAO), adenosine deaminase, and MDA activities observed in $AlCl_3$-induced rats. In addition, HS-AuNPs treatment assuaged the increased beta-secretase 1 (BACE-1) and mRNA expression of cyclooxygenase-2 (COX-2) spurred by $AlCl_3$ (Anadozie et al. 2023).

Moringa oleifera

Moringa oleifera leaf extract has also been demonstrated to protective against $AlCl_3$ toxicity by resolving pyramidal cells of CA3 and neurofibrillary tangles in the hippocampus (Finbarrs-Bello et al. 2022).

Harrisonia abyssinica

A promising candidate to alleviate aluminum-induced neurotoxicity in the hippocampus is *Harrisonia abyssinica.* In addition to having antioxidant, anti-inflammatory, and anti-apoptotic effects, *H. abyssinica* leaf extract normalizes the levels of glutamate, extracellular regulated kinase (ERK1/2), caspase-3, AChE, and catecholamines in the hippocampus of AD rats. It also helped to prevent the buildup of Aβ plaques and returned the hippocampus region of the brain tissue to its original state. These activities are most likely caused by the high polyphenol content (Anwar et al. 2021).

Orange peel

An examination of orange peel extract's neuroprotective impact *in vivo* suggests that it may be useful in reducing brain oxidative stress and preventing the progression of Alzheimer's disease. Orange peel extract protected against $AlCl_3$-induced neuronal damage via decrease in both gene expression and activity of AChE, thiobarbituric acid-reactive substances (TBARS), amyloid beta (Aβ42) protein level, and nitric oxide (NO), and increase in reduced GSH level, and activity of the antioxidant enzymes in the brain tissues. Additionally, presinilin-2 (PSEN2) and beta cell lymphoma-2 (BCL2) were upregulated, meanwhile, gene expressions for APP and beta secretase enzyme (BACE1) were downregulated (Abd El-Aziz et al. 2023).

Echinacea purpurea

Another plant that has been investigated to ameliorate the neurodegenerative effects of $AlCl_3$-induced Alzheimer's disease is *Echinacea purpurea*. *E. purpurea* flower extracts, both Aqueous (AQ) & Alcoholic (AL), inhibited AChE, downregulated interleukin-6 (IL-6) & tumor necrosis factor alpha (TNF-α), restored oxidative balance, & improved behavior performance *in vivo* and also decreased amyloid plaques & neuronal degeneration in the hippocampus & cerebral cortex (Mohamed et al. 2023).

Mentha longifolia

Methylene chloride and ethyl acetate fractions (EaFr) of *Mentha longifolia* were found to have anticholinesterase activity and reversed the $AlCl_3$-mediated MDA increase and GSH decrease. The elevated levels of nuclear factor-kappa B (NF-κB) and NO were also reversed by EaFr of *M. longifolia*. It also counteracted the $AlCl_3$ effect on brain neurotransmitters (norepinephrine, dopamine, and serotonin) (Elshamy et al. 2021).

Autranella congolensis

A potential treatment for preventing oxidative damage in AD is *Autranella congolensis*. $AlCl_3$ lowered CAT, GPx, reduced total thiol, aconitase levels, and thiol protein levels and increased protein oxidation levels & lipid peroxidation in the brain or rats, meanwhile, the extract of *A. congolensis* significantly moderated these effects (Ngoumen et al. 2023).

Ginko Biloba

Interestingly, *Ginkgo biloba* and vitamin C together constitute new therapeutic possibilities for neurodegenerative diseases, notably AD, as they were used to treat $AlCl_3$-induced neurotoxicity in rats. A study found that administering *G. biloba* methanolic leaf extract along with vitamin C improved cholinergic and dopaminergic dysfunction & alleviated memory impairment. Also, it significant improved hippocampal morphology & histopathological alterations. It turned out that *G. biloba* and/or vitamin C could exhibit an improvement in neurotoxicity & memory loss and may be a viable treatment for cognitive decline in AD patients (Elhallouty et al. 2022).

Canna indica

Canna indica is a member of the “Cannaceae” family and “Canna” genus. Numerous pharmacological studies revealed its anti-inflammatory and anti-neurodegenerative properties, as well as its impact on the AChE enzyme (Chigurupati et al. 2021). Whole plant extract from *C. indica* showed potential anti-inflammatory, anti-radical, and neuroprotective properties (Chigurupati et al. 2021). The memory-improving & neuroprotective mechanism of action of *C. indica* have recently been demonstrated in a study *in vitro* and *in vivo*. In a study, chronic *C. indica* therapy improves $AlCl_3$-induced memory damage by regulating antioxidant pathways, restoring cholinergic system activity, and increasing dopamine levels (Ojha et al. 2023).

Stachytarpheta angustifolia

The seasonal plant *Stachytarpheta angustifolia*, has been associated with neuroprotection against $AlCl_3$-induced AD. Recently, a study showed the decreased level of SOD, CAT, GPx and GSH in $AlCl_3$-induced AD were significantly increased by the methanolic whole plant

extract of *S. angustifolia*. However, it significantly decreased NO, MDA, COX-2, & AChE (Ashikaa et al. 2023). The presence of phenol, saponin, alkaloid, flavonoid, and terpenoid with potent antioxidant, anti-inflammatory, & AChE inhibitory characteristics may be responsible for the neuroprotective effect of the extract. As a result, the extract has the potential to be an effective medication source for the treatment and management of AD disease (Ashikaa et al. 2022).

Annona squamosa

The recovery of the behavioural and biochemical changes caused by $AlCl_3$ and the strong neuroprotective mechanism of *Annona squamosa* against AD were both demonstrated by the ethanol extract of *A. squamosa* fruit pulp (Muthusamy et al. 2023). However, this is most likely due to the powerful antioxidant capabilities of the fruit pulp, which effectively counteract oxidative stress and maintain transmembrane protein levels.

Bryophyllum pinnatum

The significant perennial herb *Bryophyllum pinnatum* (Crassulaceae) is widely used to cure a variety of diseases. The enriched flavonoid fraction of the leaves of *B. pinnatum* reduced oxidative imbalance by strengthening antioxidant defense and decreasing $AlCl_3$-induced lipid peroxidation. It downregulated AChE mRNA transcripts & improved histological features in the cortex & hippocampus. These points to the neuroprotective effect of *B. pinnatum* against $AlCl_3$-induced neurotoxicity (Ogidigo et al. 2022).

Sesamum indicum

In a study, $AlCl_3$-induced learning and memory impairments were significantly improved by sesame (*Sesamum indicum*) oil. The elevated level of AChE and Aβ overexpression were also significantly reduced after treatment with sesame oil. Moreover, $AlCl_3$ treatment resulted in histopathological changes, an increase in the expression of TNF-α and interleukin-1 beta (IL-1β), as well as mitigation of oxidative stress status in the brain. All of these anomalies were eliminated by sesame oil. Meanwhile, it also inhibited $AlCl_3$-induced activation of p38 mitogen-activated protein kinase (p38MAPK) and the decrease in brain-derived neurotrophic factor (BDNF). Additionally, treated with sesame oil modulated the expression of the nuclear factor kappa B (NF-κB) and peroxisome proliferator-activated receptor gamma (PPAR-γ). Interestingly, many studies have shown that sesame oil is unique because it contains a significant amount of bioactive antioxidant lignans, particularly sesamolin, sesamin, sesamolinol, and sesaminol (Mohamed et al. 2021).

Rosa damascena

The Crassulaceae family includes *Rosa damascena* (Damask Rose), which grows in Northern Asia and the mountains of Central Europe. In AD rats, administration of the *R. damascena* extract enhanced CAT and GSH levels, decreased MDA levels, and regulated AChE activity. These demonstrate that *R. damascena* extract is protective against the oxidative damage caused by $AlCl_3$ intoxication (Hejaziyan et al. 2023).

Tamarindus indica

According to phytochemical analysis of *Tamarindus indica* (which belongs to the monotypic genus Tamarind), there are several significant bioactive components present in this plant, including phenolic compounds, glycosides, malic acid, tartaric acid, arabinose, pectin, mucilage, xylose, galactose, glucose, and uronic acid (Usman et al. 2022). During exposure to $AlCl_3$, *T. indica* reduced the levels of pro-inflammatory cytokines and lipid peroxidation products in the cerebral cortex. *T. indica* also protected against aluminum chloride induced memory impairment (Muhammad et al. 2020). The improvement in oxidative stress biomarker, spatial memory and learning, and glial fibrillary acid protein reactivity confirmed that the administration of ethyl acetate leaf fraction of *T. indica* was of therapeutic value during prenatal $AlCl_3$ exposure in Wistar rats (Usman et al. 2022). Moreover, following prenatal $AlCl_3$ exposure in Wistar rat pups, the ethyl acetate fraction of *T. indica* leaves also significantly increased calcium levels and decreased mean zinc, copper, and iron levels. Additionally, it enhanced cognition and increased brain sialic acid (Usman et al. 2023).

Vaccinium corymbosum

The Ericaceae family plant *Vaccinium corymbosum*, widely known as the blueberry, may have an effect on human health and wellbeing as well as provide neuroprotection **(**Hong et al. 2018; Miller et al. 2019**)**. The fruits of blueberry trees, in particular, are high in polyphenols and flavonoids. In a behavioural study, rats treated with ethanolic extracts of *V. corymbosum* demonstrated neuroprotective effects against $AlCl_3$-induced neurotoxicity along with a significant decrease in AChE enzyme. The neuroprotection of *V. corymbosum* makes it a promising therapeutic agent for treating behavioral and cognitive dysfunctions (Chellammal et al. 2021).

Xylopia parviflora

Xylopia parviflora has antioxidant and anti-inflammatory properties (Nwakiban et al. 2020; Nwakiban et al. 2021). According to a study, the fruit extract from *X. parviflora* effectively improved all alterations caused by Al. Treatment with *X. parviflora* in various dosages improved memory and locomotion, ion homeostasis, cholinesterase activities, and stabilized brain oxidative stress levels. According to the study, *X. parviflora* may be useful for the management of some biochemical alterations linked to AD. It may be beneficial in neurotoxicity caused by Al at the behavioural and biochemical levels. *X. parviflora* may have promising

compounds that could be tested as potential drugs for the treatment of diseases caused by oxidative stress and cholinergic dysfunction like AD due to its combination of antioxidant, anti-cholinesterase potential, and improvement of cognitive impairment (Dibacto et al. 2022).

Pluchea lanceolata

In a study, $AlCl_3$ increased protein content and MDA, and reduced body weight, CAT, SOD, & GSH levels. These effects were reversed and restored by *Pluchea lanceolata* hydromethanolic extracts. The hydromethanolic extracts of *P. lanceolata* also offered cellular-level protection, according to the histopathology findings. As a result, the active components of *P. lanceolata* were found to have anti-Alzheimer and antioxidant potential (Asirvatham et al. 2022).

Salvia officinalis

In addition to a significant increase in the serum levels of urea, creatinine, AST, and ALT activity as well as oxidative stress indicators, $AlCl_3$-induced AD rats showed significant alterations in Tau protein and acetylcholine levels in brain tissue. However, administration of *Mg-Salvia officinalis nanoparticles (NPs)* significantly improved all previous parameters. In conclusion, treatment with *S. officinalis NPs* ameliorated oxidative stress, enhanced antioxidant defense system, and prevented the lipid peroxidation caused by $AlCl_3$. So, administration of Mg-*Salvia officinalis* NPs for the treatment of AD can be recommended (Elkomy et al. 2021).

Vanda tessellate

Vanda tessellate can be used as a remedy for the treatment of AD and neurotoxicity. A study revealed that, the hydromethanolic extract of *V. tessellate* was able to correct and restore the increased level of protein content, MDA, reduction in body weight & antioxidants enzymes including CAT, SOD, and GSH that were caused by $AlCl_3$ administration. The histopathological report also demonstrated the cellular level protective efficacies of the *V. tessellate* hydromethanolic extract. It should be emphasized that the active constituents present in *V. tessellate* was responsible for its neuroprotective effects (Salam et al. 2022).

Grape seed oil

Grape seed (*Vitis vinifera*) oil reduced $AlCl_3$-induced significant decline in cognitive function, and significantly decreased AChE and modulated antioxidant (SOD, CAT, glutathione reductase) activity level. Additionally, histopathological studies in the hippocampus and cortex supported the fact that grape seed oil significantly decreased $AlCl_3$ toxicity. Grape seed oil supplementation exhibited a positive and neuroprotective role $AlCl_3$-induced neurotoxicity in Wistar rat by enhancing cognitive memory and antioxidant enzyme levels (Muralidharan and Swetha 2023).

Zingiber officinale

Studies conducted have noted the anti-inflammatory (Tongshuwar et al. 2020; Ojetunde et al. 2021) and antioxidant capacity (Bekkouch et al. 2022) of the active components in *Zingiber officinale* (ginger). The use of *Z. officinalis* as a therapeutic approach against neurological diseases has great potential. In a study, the use of *Z. officinalis* ethanol extract and its fraction (Dichloromethane and n-hexane) improved memory and decreased oxidative stress status in $AlCl_3$-induced mice (Inwang et al. 2023).

Bougainvillea spectabilis

The flower decoction of Bougainvillea spectabilis may be useful in the treatment of AD. According to research, *B. spectabilis* alleviated the increase in NO and MDA, and decrease in GSH and PON-1 activity alterations evoked by $AlCl_3$. Also, *B. spectabilis* decoction significantly reduced IL-6 and Aβ in the brain of rats treated with $AlCl_3$. It also protected against neurodegeneration induced by $AlCl_3$, & restored memory performance and motor strength (Abdel-Salam et al. 2021).

Peganum harmala

In North Africa, *Peganum harmala*, a traditional plant from the Zygophyllaceae family, is commonly referred to as Harmal or Haramlaan (Asgarpana and Ramezanloo 2012; Eissa et al. 2014). *P. harmala* has abundance of β-carboline alkaloids, with the seeds having the highest quantitiy (Osman et al. 2018; Araujo et al. 2019). These include harmaline, harmine, harmalol, harmane, and norharmane (Osman et al. 2018). Harmine and harmaline have AChE inhibitory effect and antioxidant activity, which suggests that they may be used to treat AD (Ali et al. 2013). In a study, *P. harmala* improved cognition and histopathological features altered by $AlCl_3$. Additionally, it increased the hippocampus level of insulin & glucagon-like peptide (GLP)-1, while decreasing the phosphorylation of insulin receptor substrate-1 at serine 307 (*p*S307-IRS-1). Besides, phosphorylated Akt at serine 473 (*p*S473-Akt) and glucose transporter type (GLUT)4 were also increased by *P. harmala*. The levels of (Aβ)42, glycogen synthase (GSK)-3β and phosphorylated tau in the hippocampus were also reduced by the extract. Along with lowering lipid peroxides and replenishing glutathione, *P. harmala* also improved nuclear factor erythroid 2-related factor 2 (Nrf2) (Saleh et al. 2021).

Vernonia amygdalina

The plant *Vernonia amygdalina* belongs to the Asteraceae family. It is commonly referred to as "bitter

leaf plant" (Ojetunde, 2021). Phytochemical components of *V. amygdalina* include epivernodalol, lactones, sesquiterpene, elemanolide, terpenes, edotides, steroids, flavonoids, coumarins, phenolic acids, xanthones, lignans, saponins, anthraquinone, & alkaloids (Muraina et al. 2010). *V. amygdalina* has been scientifically proven to be effective against a variety of disease due to its high antioxidant content. *V. amygdalina* leave extract significantly improved hippocampal histological features and reduced the behavioral abnormalities in rats caused by $AlCl_3$. However, in the treatment of AD, *V. amygdalina* perform better as a preventive than as a curative (Ajeleti et al. 2023).

Lepidium sativum

Lepidium sativum (family: Brassicaceae) is used as a treatment for a variety of diseases and has a wide range of pharmacological properties, such as antioxidant, anti-inflammatory, & anti-diabetic activity (Attia et al. 2019). Administration of *L. sativum* significantly enhanced antioxidant parameters, decreased pro-inflammatory cytokines, and attenuated AD-related histopathological alterations (Balgoon 2023).

Buchholzia coriacea

Buchholzia coriacea plant belongs to the family *Capparaceae* (Obembe et al. 2012). *B. coriacea* has been proven to have neuroprotective properties (Abayomi et al. 2019). Its phytochemical constituents include saponin, reducing sugar, alkaloids, glycosides, tannin, flavonoids, terpenes, steroid, & phenols (Ibrahim and Fagbohun 2013). The presence of flavonoids, vitamins, antioxidant, and enzymes may be largely responsible for its therapeutic effects (Ibrahim and Fagbohun 2013). According to research, *B. coriacea* significantly enhanced spatial working memory, and restored myelin sheath integrity, both of which would inevitably speed up impulse conduction and improve the memory process in AD (Adelodun et al. 2021).

Rosmarinus officinalis

Rosmarinus officinalis (Rosemary) belongs to the Lamiaceae family and has high phenolic and terpenoid compounds (Andrade et al. 2018). It has anti-inflammatory, antioxidant, and antidepressant properties (Guo et al. 2018; Dabaghzadeh et al. 2022). In addition to improving cognition, *R. officinalis* can regulate synaptic gene expression, inflammation, and the density of hippocampal neurons in $AlCl_3$-induced neurotoxicity (Khalid et al. 2020). In an animal model of AD, it has been proven that *R. officinalis* can significantly improve cognitive impairment, and significantly lower depression and anxiety. *R. officinalis* improved cognitive function but did not decrease the burden of amyloid plaque, suggesting that the memory-enhancing effects of this plant are caused by a different mechanism that needs to be investigated (Malik et al. 2022).

Massularia acuminata

Massularia acuminate (family: Rubiacea) significantly reduced MDA levels in animals treated with $AlCl_3$. On the other hand, the same level of SOD and CAT was shown in animals that were treated with *M. acuminate* with level of ascorbic acid in $AlCl_3$-induced toxicity. However, butanolic extract of *M. acuminata* at 50 mg/kg and 100 mg/kg body weight show that they cause oxidative stress because they increase MDA level. As a result, the ethanolic and methanolic stem extract of *M. acuminata* can act as potential antioxidant compounds in the treatment of oxidative stress related to $AlCl_3$ toxicity (Bakare et al. 2021).

Capsicum annuum

The most consumed spices in the world are hot red or green peppers of the plant genus *Capsicum* (*Capsicum annuum* and *Capsicum frutescens*) (Abdel-Salam et al. 2023). In experimental models of Parkinson's disease, studies have that hot pepper extracts have neuroprotective effects (Abdel-Salam et al. 2018). Moreover, it has been noted that consuming capsaicin-rich diet improves cognition and lower Aβ levels in the serum of adults (Liu et al. 2016). In the APP/PS1 genetic mice model of AD, similar findings were reported (Wang et al. 2020). Thus, *Capsicum* may be a beneficial nutraceutical to prevent and/or delay neurodegeneration in the brain of AD patients. In a study, rats treated with $AlCl_3$ received methanolic extract of *Capsicum* fruits (hot red peppers), which significantly reduced oxidative stress (decreased NO & MDA, and increased GSH and PON-1 levels) as well as Aβ-peptide and IL-6 in the brain. *Capsicum* fruits also improved grip strength and memory functioning and prevented neuronal degeneration in the hippocampus, cerebral cortex, and substantia nigra of rats treated with $AlCl_3$ (Abdel-Salam et al. 2023).

Benincasa hispida

Benincasa hispida (ash gourd or wax gourd) modulated the levels of dopamine, serotonin, & AChE in $AlCl_3$-induced AD. The extract of *B. hispida* leaves increased SOD, CAT, GSH and decreased MDA levels. *B. hispida* treatment also decreased the levels of TNF-α & IL-1β in AD. *It* further upregulated antioxidant genes Keap/Nrf2/HO-1. Histopathological examinations of the hippocampus further confirmed the neuroprotective potential of *B. hispida* (Rapaka et al. 2021). *B. hispida* is thus a potential substitute for neuroprotection in the treatment of AD.

Euphorbia cotinifolia

The methanol extract of *Euphorbia cotinifolia* significantly improved motor dysfunctions and cognitive abilities of animals with AD. The levels of ACh, SOD, CAT, GPx, and GSH were also elevated by the treatment with the methanol extract of *E. cotinifolia*. Histopathological analysis revealed less neurofibrillary

tangles and neuronal loss. *E. cotinifolia* methanol extract also reduced the expression of IL-1α, IL-1β, TNF-α, & TNF-β in AD animals (Saadullah et al. 2023).

Punica granatum

Pomegranate plant (*Punica granatum*) contains unique components like flavonols, ellagitannins, phenolic acids, anthocyanins, & organic acids, which have antioxidant, antineurodegenerative, anticancer, anti-inflammatory and anti-apoptotic activities (Ahmadiankia 2019; Kandylis and Kokkinomagoulos 2020). *P. granatum* has antioxidant levels that are two, six, and eight times higher than those of red berries, grapefruit, and orange juice respectively (Abu-Taweel and Al-Mutary 2021). Pomegranate helps to prevent cognitive and behavioral decline in AD (Subash et al. 2015). In a study, *P. granatum* juice significantly improved body weight, spatial memory and learning, neurotransmitters and oxidative biomarkers in the $AlCl_3$-treated mice (Abu-Taweel and Al-Mutary 2021).

Phyllanthus amarus

Phyllanthus amarus, a commonly used medicinal plant, have some reported antioxidant properties. In a study, $AlCl_3$ significantly decreased the survival rate, climbing activity, SOD, GST, CAT activities and increased MDA concentration and AChE activities in *Drosophila melanogaster*. However, *P. amarus* was able to significantly ameliorate all these changes. *P. amarus* can therefore have therapeutic benefits in the management of AD (Inneh and Enogieru 2023).

Centella asiatica

A perennial herbaceous creeper, *Centella asiatica* (family: Apiaceae), is locally referred to as pegaga in Malay (Chiroma et al. 2017; Gray et al. 2018). In the Ayurvedic system of medicine, *C. asiatica* is regarded as invigorating herb that improves memory and intelligence. The medicinal values of *C. asiatica* are connected to its numerous active constituents such as madecassic acid, asiatic acid, asiaticoside, braminoside, madecassoside, bramoside, and flavonoids (Gohil et al. 2010). *C. asiatica* prevented $AlCl_3$-induced cognitive impairment of both spatial and non-spatial memory, histopathological aberration of the cerebral cortex, and increased levels of AChE in the brain of rats (Farhani et al. 2023). Thus, it could be developed as a memory enhancing drug.

Onion and garlic

According to several studies, consuming onion flavonoid containing quercetin protects brain tissues from aging by inhibiting apoptosis that causes brain degeneration (Wang et al. 2020; Dorrigiv et al. 2021). Moreover, the active components found in garlic extracts have been shown to have protective effects against neurotoxicity (Galal et al. 2019; Hazzaa et al. 2020; Bigham et al. 2021). In a recent study, intracellular ROS generation in the brain of AD-induced rats was inhibited by treated with several doses of onion and garlic root extracts, which also reduced histopathological lesions, the expression levels of apoptotic genes, and the rate of DNA damage in the brain tissues (Hegazy et al. 2022).

Malva neglecta

Malva neglecta (family: Malvaceae) is an annual herbaceous species. *In vitro* studies showed that the methanolic extract of *M. neglecta* have anticholinesterase activity (Abbas et al. 2017). The presence of 25 bioactive polyphenolics was identified by HPLC-DAD analysis (Saleem et al. 2020), with hydroxytyrosol and coumaroylhexoside being in highest concentrations. These bioactive compounds have a variety of biological properties (Ren et al. 2017, Winter et al. 2017; Karković Marković et al. 2019; Khan et al. 2020) which may help explain the neuroprotective potentials of the plant. *M. neglecta* has antioxidant capacity, making it a key target in neurodegenerative disorders caused by free radicals (Dalar et al. 2012). *Malva parviflora*, another species of the family, is said to have protective against AD induced by Aβ (Aslam and Sial 2014). Study has shown that *M, neglecta* can reduce the symptoms of AD by improving memory and cognition, & modulating oxidative stress biomarkers and AChE activity (Saleem et al. 2021).

Table 1. Neuroprotective and Therapeutic Effects of Medicinal Plants against Aluminium Chloride-Induced Alzheimer's Disease.

Medicinal plant	Dose of $AlCl_3$	Dose of Extract	Animals used	Mechanism of Action	Ref
Acacia catechu	100 mg/kg b.wt. daily for 60 days orally	3 mg/kg/day i.p. on daily basis for 15 days after $AlCl_3$ administration	Rats	Antioxidant, anticholinesterase, preserved monoamines level, reduced genotoxicity, & corrected cognitive behavioral dysfunction	(Elmorsy et al. 2021)
Hibiscus sabdariffa	7 mg/kg b.wt./day i.p. for 28 days	250, 500, or 1000 mg/kg b.wt./day/p.o. for 28 days	Rats	Antioxidant, anticholinesterase	(Efosa et al. 2023)
Moringa oleifera	100 mg/kg orally for 21 days	400 mg/kg orally for 21 days	Rats	Protected against brain damage	(Finbarrs-Bello et al. 2022)

Table 1. *Cont.*

Medicinal plant	Dose of $AlCl_3$	Dose of Extract	Animals used	Mechanism of Action	Ref
Harrisonia abyssinica	100 mg/kg b.wt./day p.o.	100 or 200 mg/kg b.wt./day intragastrically for 3 weeks.	Rats	Antioxidant, anticholinesterase, anti-inflammatory, anti-apoptotic, anti-Aβ, regulated neurotransmitters level, & enhanced learning and memory	(Anwar et al. 2021)
Orange peel extract	70 mg/kg b.wt./day i.p. for 6 weeks	100 or 200 mg/kg orally for 6 weeks	Rats	Antioxidant, anticholinesterase, anti-Aβ,	(Abd El-Aziz et al. 2023)
Echinacea purpurea	175 mg/kg $AlCl_3$ orally for 60 days	250 mg/kg orally for 60 days	Rats	Antioxidant, anticholinesterase, anti-inflammatory, anti-Aβ, & improved behavior performance	(Mohamed et al. 2023)
Mentha longifolia	100 mg/kg b.wt. for 30 consecutive days by s.c. injection	250 mg/ kg b.wt./day of the fractions orally for 15 days & 100 mg/kg b.wt./day of the oil orally for 15 days before induction of AD	Rats	Antioxidant, anticholinesterase, anti-inflammatory, & regulated neurotransmitters levels	(Elshamy et al. 2021)
Hibiscus sabdariffa	100 mg/kg b.wt. orally for 42 days	5 or 10 mg/kg b.wt. for 42 days	Rats	Antioxidant, anticholinesterase, improved memory and learning, & modulated gene expression	(Anadozie et al. 2023)
Autranella congolensis	50 mg/kg b.wt. orally for 8 weeks	150 or 300 mg/kg (1hr after $AlCl_3$) orally for 8 weeks	Rats	Antioxidant	(Ngoumen et al. 2023)
Ginko biloba	17 mg/kg b.wt. for 4 weeks orally	400 mg/kg b.wt. orally for 2 weeks after 4 weeks intoxication with $AlCl_3$	Rats	Attenuated memory impairment & improved dopaminergic and cholinergic dysfunction	(Elhallouty et al. 2022)
Canna indica	17 mg/kg p.o. for 21 days	Aerial methanolic extract (200 mg/kg p.o.) or Root hydroalcholic extract (200 mg/kg p.o.) or the combination for 21 days	Rats	Antioxidant, anticholinesterase, improved memory damage, and modulated neurotransmitter level	(Ojha et al. 2023)
Stachytarpheta angustifolia	100 mg/kg b.wt. orally for 8 weeks	25, 50, or 75 mg/kg orally for 8 weeks	Rats	Antioxidant, anticholinesterase, & modulated cognitive functions	(Ashikaa et al. 2023)
Annona squamosa	17 mg/kg b.wt. for 30 days orally	200 or 400 mg/kg b.wt. for 60 days after administration of $AlCl_3$ for 30 days	Rats	Antioxidant, anticholinesterase, & enhanced cognitive functions	(Muthusamy et al. 2023)
Bryophyllum pinnatum	150 mg/kg b.wt. orally for 21 days	50 or 100 mg/kg b.wt. orally for 21 days (after administration of $AlCl_3$ for 21 days)	Rats	Antioxidant, anticholinesterase, & restored histopathological lesions	(Ogidigo et al. 2022)
Sesamum indicum	100 mg/kg/i.p. for 6 weeks	1 ml/kg or 2 ml/kg, p.o. for 6 weeks	Rats	Antioxidant, anti-inflammatory, anticholinesterase, anti-Aβ, & improved learning and memory	(Mohamed et al. 2021)

Table 1. *Cont.*

Medicinal plant	Dose of $AlCl_3$	Dose of Extract	Animals used	Mechanism of Action	Ref
Rosa damascena	100 mg/kg orally for 4 weeks	500 or 1000 mg/kg orally for 8 weeks and $AlCl_3$ orally daily for the last 4 consecutive weeks.	Rats	Antioxidant, anticholinesterase, & improved learning & memory	(Hejaziyan et al. 2023)
Tamarindus indica	200 mg/kg b.wt. orally 14 days from prenatal day 7 till parturition	400 mg/kg or 800 mg/kg b.wt. orally for 14 days from prenatal day 7 till parturition	Rats	Antioxidant, improved glial fibrillary acid protein reactivity & spatial memory & learning	(Usman et al. 2022)
Vaccinium corymbosum	100 mg/kg orally for 42 days	200 or 400 mg/kg on the 21st day until the 42nd day	Rats	Anticholinesterase, & mitigated behavioural & cognitive dysfunctions	(Chellammal et al. 2021)
Xylopia parviflora	75 mg/kg by oesophageal gavage for 60 days	150 or 300 mg/kg b.wt. by oesophageal gavage for 60 days	Rats	Improvement of cognitive impairment, antioxidant, & anti-cholinesterase	(Dibacto et al. 2022)
Pluchea lanceolata	300 mg/kg, p.o. for 20 days	200 or 400 mg/kg, p.o. for 20 days	Rats	Antioxidant, cellular-level protection, & raised the level of neurotransmitters	(Asirvatham et al. 2022)
Salvia officinalis	100 mg/kg b.wt./i.p. for 2 weeks	5 mg/kg b.wt./day, orally for 4 weeks (After 14 days of $AlCl_3$ injection)	Rats	Antioxidant, decreased brain Tau protein level, & increased brain ACh	(Elkomy et al. 2021)
Vanda tessellate	300 mg/kg, p.o. for 20 days	300 mg/kg, p.o.	Rats	Antioxidant, histological cellular-level protection, & raised the level of neurotransmitters	(Salam et al. 2022)
Tamarindus indica	200 mg/kg b.wt. orally 14 days from prenatal day 7 till parturition	400 mg/kg or 800 mg/kg b.wt. orally for 14 days from prenatal day 7 till parturition	Rats	Improved memory & learning, trace element, & brain sialic acid concentration	(Usman et al. 2023)
Grape seed oil	175mg/kg p.o. for 30 days	2ml (3.7g/kg) or 4ml (3.7g/kg) p.o. on the 20th day of experiment for 10 days	Rats	Anti-oxidant, anti-cholinesterase, alleviates impaired cognitive function	(Muralidharan and Swetha 2023)
Zingiber officinalis	100 mg/kg orally for 3 weeks	Ethanol extract (474, 949 or 1,423 mg/kg), dichloromethane extract (949 mg/kg) & n-hexane extract (949 mg/kg)	Mice	Antioxidant, memory improvement	(Inwang et al. 2023)
Bougainvillea spectabilis	10 mg/kg i.p. for 2 months	50 or 100 mg/kg i.p. daily during the 2nd month	Rats	Antioxidant, anti-inflammatory, anti-amyloid, restored motor and memory impairment, histological neuroprotection.	(Abdel-Salam et al. 2021)
Peganum harmala	50 mg/kg/day i.p. for 6 consecutive weeks	187.5 mg/kg; p.o starting 2 weeks post $AlCl_3$ exposure for 4 weeks	Rats	Antioxidant, anti-Aβ, enhanced cognition, & ameliorated hippocampal insulin resistance	(Saleh et al. 2021)
Vernonia amygdalina	0.43 mL/kg via oropharyngeal cannula for 14 days	1.31 mL for 14 days before or after $AlCl_3$ administration for 14 days	Rats	Improved memory & hippocampal histological features	(Ajeleti et al. 2023)

Table 1. *Cont.*

Medicinal plant	Dose of $AlCl_3$	Dose of Extract	Animals used	Mechanism of Action	Ref
Lepidium sativum	10 mg/kg b.wt. i.p. for 8 weeks	20 mg/kg via gavage for 4 weeks after $AlCl_3$ administration for 4 weeks	Rats	antioxidant, anti-inflammatory, anti-apoptotic, anti-Aβ, anticholinesterase, & alleviated histopathological changes	(Balgoon 2023)
Buchholzia coriacea	200 mg/kg orally for 14 days	50 or 100 mg/kg orally for 14 days	Rats	Improved spatial working memory and histological changes	(Adelodun et al. 2021)
Rosmarinus officinalis	300 mg/kg for 15 days	100 mg/kg i.p. for 10 days after 15 days of $AlCl_3$	Mice	Improved memory impairment, and decreased anxiety & depression	(Malik et al. 2022)
Massularia acuminata	34 mg/kg orally for 3 weeks	50 or 100 mg/kg orally for 3 weeks	Rats	Antioxidant	(Bakare et al. 2021)
Capsicum annuum	10 mg/kg i.p. for 60 days	25 or 50 mg/kg i.p. during the 2nd month of the study	Rats	Antioxidant, anti-Aβ, anti-inflammatory, & improved memory impairment and neuromuscular strength	(Abdel-Salam et al. 2023)
Benincasa hispida	100 mg/kg/day orally for 8 + 16 weeks	250 or 500 mg/kg/day orally for 16 weeks after $AlCl_3$ administration for 8 weeks	Rats	Antioxidant, anti-inflammatory, anti-Aβ, & improved memory and neurotransmitters level	(Rapaka et al. 2021)
Euphorbia cotinifolia	300 mg/kg p.o. for 21 days	100, 300, or 800 mg/kg p.o. for 21 days	Rats	Antioxidant, anti-inflammatory, anticholinesterase, & improved cognitive behaviours	(Saadullah et al. 2023)
Punica granatum	400 mg/kg orally for 35 days	20% or 40% orally for 35 days	Mice	Antioxidant, modulated neurotransmitters level, reduced cognitive impairment, & enhanced spatial learning & memory capacity	(Abu-Taweel and Al-Mutary 2021)
Phyllanthus amarus	40mM via diet	2.5mg via diet	*Drosophila melanogaster*	Antioxidant and anticholinesterase	(Inneh and Enogieru 2023)
Centella asiatica	70 mg/kg b.wt. i.p. for 42 days	200, 400 or 800 mg/kg b.wt. for 42 days	Rats	prevented cognitive impairment, anticholinesterase	(Farhani et al. 2023)
Onion and garlic	0.3% for 45 days	1, 2, or 3 mg/kg onion extract; 1, 2, or 3 mg/kg garlic extract for 30 days (after 45 days of $AlCl_3$ treatment)	Rats	Antioxidant, anti-apoptotic, decreased histopathological lesions & the rate of DNA damage	(Hegazy et al. 2022)
Malva neglecta	100 mg/kg orally for 21 days	200, 400 or 600 mg/kg orally for 21 days	Rats	Antioxidant, anti-cholinesterase, and improved memory and cognition	(Saleem et al. 2021)

Note: $AlCl_3$: Aluminium Chloride; Aβ: Amyloid-beta; AD: Alzheimer's disease; ACh: Acetylcholine; b.wt.: body weight; i.p.: intraperitoneally; p.o.: Oral administration; s.c.: subcutaneous

ROLE OF NATURAL PRODUCTS AGAINST ALUMINIUM CHLORIDE-INDUCED ALZHEIMER'S DISEASE

Phytochemicals

Morin, thymol, and thymoquinone are phytochemicals that, when combined with physical and mental activities (PhM), restored antioxidant activities, increased heme oxygenase-1 (HO-1) and Nrf2 levels, blocked inflammasome activation, TLR4 expression, apoptosis, Aβ generation, and tau hyperphophorylation. Additionally, they restored the levels of ApoE4 and LRP1 and regulated the Wnt3/β-catenin/GSK3β signaling pathway. Therefore, the combination of phytochemicals with PhM is a promising strategy for reducing AD (Hamdan et al. 2022).

Niruriflavone

Niruriflavone, a compound isolated from *Phyllanthus niruri*, reversed $AlCl_3$-induced neurobehavioral alteration. The niruriflavone treatment also reduced AChE and lipid peroxidation, and restored the antioxidative enzymes (Rajamanickam and SL 2022).

Quercetin

Administration of quercetin attenuated behavioral deficits, ameliorated dopaminergic & cholinergic dysfunctions, and diminished the aggregation of insoluble Aβ plaques in the hippocampus of $AlCl_3$-induced AD rat. Quercetin downregulated APP, BACE1, anterior pharynx-defective 1 (APH1), & PSEN1, meanwhile upregulated ADAM10 and ADAM17 gene expression levels in the hippocampus, leading to amyloidogenic pathway inhibition. In order to counteract Aβ aggregation & cognitive deterioration in AD, it has been hypothsized that ADAM10 (A Disintegrin and Metalloproteinase 10) and ADAM17 (A Disintegrin and Metalloproteinase 10) activation may be potential therapeutic targets (Elfiky et al. 2021). According to a similar study, quercetin significantly affects memory deficits in AD. Furthermore, quercetin significantly decreased APP, BACE1, and PSEN1 and increased ADAM17 expression in the hippocampal tissue of AD rats (Elreedy et al. 2023).

Similarly, significant improvement in behavioral parameters, inhibition of AChE activity, and decrease in oxidative stress parameters (significantly higher levels of GSH, CAT, & SOD, as well as lower levels of MDA) have all be have all been seen when quercetin was combined with memantine. After treatment of quercetin with memantine, histopathological examination of the hippocampus and cortex showed a decrease in the formation of Aβ plaque. According to immunohistochemistry, the combination of quercetin and memantine also improved the expression of BDNF and inhibited the formation Aβ plaque (Jadhav and Kulkarni 2023a). Quercetin has been linked to a variety of therapeutic actions, including antioxidant, anti-amyloidogenic, anti-inflammatory, and neuroprotective effects (Kim and Park 2018). The neuroprotective effects of quercetin are due to its capacity to inhibit xanthine oxidase and prevent lipid peroxidation or scavenge oxygen (Jadhav and Kulkarni 2023a). Additionally, quercetin has been shown to have neurotropic effect by regulating the Akt/PKB (protein kinase B) and ERK1/2 signaling pathway by impeding the activity of PI3K (phosphoinositide 3-kinase) (Minocha et al. 2022). Quercetin nanoemulsion also provided protection against neuronal dysfunction caused by $AlCl_3$ via the elevation of brain antioxidants, reduction of the production of pro-inflammatory cytokines, and modulation of neurotransmitter levels, and reversing the histopathological changes in rats (Alaqeel et al. 2022).

Resveratrol

In a study, the combination of resveratrol and tannic acid significantly reduced AD-related cognitive decline. This treatment significantly reduced oxidative stress markers and the levels of amyloid found in AD. This demonstrated protective benefit of combination of resveratrol and tannic acid in $AlCl_3$-induced neurotoxicity (Bhounsule and Bhatt 2023). Also, Resveratrol-Selenium nanoparticles (RSV-SeNPs) supplementation attenuated oxidative markers impairement and mitochondrial dysfunction in AD. RSV-SeNPs ameliorated cholinergic deficits and also cleared Aβ. Furthermore, activation of PI3K deactivates glycogen synthase kinase 3 beta (GSK-3β)-mediated tau hyperphosphorylation. Additionally, RSVSeNPs alleviated neuroinflammation in AD by downregulating signal transducer and activator of transcription (STAT3) expression, and IL-1β levels. Moreover, Sirtuin-1 (SIRT1) was upregulated and microRNA-134 expression was downregulated by RSVSeNPs, which increases neurite outgrowth (Abozaid et al. 2022). Furthermore, the administration of RSV-SeNPs improved neuronal transmission in AD by decreasing oxidative stress and metal chelation while also increasing neurotransmitter levels (AboZaid et al. 2021).

Thymoquinone

Thymoquinone and celastrol may also be an effective therapy for neurodegenerative diseases caused by oxidative stress and neuroinflammation as well as $AlCl_3$-induced neurotoxicity. A recent study showed that thymoquinone and celastro significantly reversed the impairment of motor coordination, reduction of free ambulation, reduction of whole-brain ACh, dopamine, and serotonin concentrations. Administration of the combination also reversed the reduction of total antioxidant capacity (TAC), increment of MDA accumulation, elevation of TNF-α and IL-6, and suppression of BDNF mRNA expression linked to $AlCl_3$-induced AD (Abbas et al. 2022).

Betalain

Betalain, a glycoside pigment widely present in beetroot, mushrooms, pear, Swiss chard, prickly dragon fruit, and tubers, has been reported to mitigate $AlCl_3$-induced AD via modulating the activation of NF-κB pathway. It improved memory and learning capacity, and suppressed lipid oxidation (MDA) via the regulation of antioxidant content (SOD, CAT, and GSH). It also inhibited $AlCl_3$–induced lactate dehydrogenase (LDH), NO, AChE, & transmembrane protein (Na^+K^+ATPase) activity. In addition, betalain decreased NF-κB associated mRNA expression (TNF-α, IL-1β, IL-6, COX-2, iNOS) (Shunan et al. 2021).

Vinpocetine

In clinical settings, vinpocetine, a semi-synthetic vincamine derivative, is used to treat dementia and memory disturbances. Vinpocetine has several functions, including antioxidant, anti-inflammatory, and vasodilation therapeutic actions (Zhang et al. 2018). In rats, vinpocetine combined with epigallocatechin-3-gallate (EGCG) protected neurons against $AlCl_3$–induced AD. This combination significantly decreased Aβ, & AChE levels. The levels of monoamines and BDNF showed similar patterns of result. In addition, the combination demonstrated more prominent anti-inflammatory (IL-1β, TNF-α) and antioxidant (MDA, SOD, TAC) effects (Ali et al. 2022).

β-sitosterol

Treatment with β-sitosterol reduced $AlCl_3$-induced cognitive impairment. In a study, β-sitosterol significantly increased step-through latency time, percentage alteration time, percentage preference index, ACh, & GSH levels, and lowered the levels of AChE in $AlCl_3$-induced AD in mice. β-sitosterol also significantly reduced Aβ deposition caused by $AlCl_3$ (Yadav et al. 2023).

Gallic acid and hesperidin

Gallic acid is a common plant metabolite having several hydrogen atoms in its phenolic structure that easily delocalize free radicals (Kahkeshani et al. 2019). Gallic acid exerts its neuroprotective effects via preventing N-methyl D-aspartate (NMDA) receptors activation, and the release of glutamate, as well as inhibiting amyloid-induced neurotoxicity by selectively suppressing the activation of NF-κB (Gao et al. 2019; Bai et al. 2021). Hesperidin restored antioxidant enzymes levels in biological systems. Hesperidin and its derivatives have been shown to have antioxidant potential due to their structures which abound in hydroxyl groups (Kim et al. 2019; Stanisic et al. 2020). The ability of hesperidin to inhibit oxidative stress, apoptosis, inflammation, and amyloid polymerization shows that it's a promising potential in the treatment of AD (Wdowiak et al. 2022). In a study, gallic acid & hesperidin were both found to significantly protect against $AlCl_3$–induced AD, suggesting their consumption may be important to delay the onset of the disease. The study showed that gallic acid or hesperidin administration prevented cognitive impairment. Additionally, gallic acid or hesperidin significantly prevented deficits in neurotransmission (AChE, BChE, serotonin, norepinephrine, and dopamine), oxidative stress (SOD, GSH, CAT, and GST), and inflammation (IL-6, IL-1β, & TNF-α), while also lowering brain caspase-3 level. The findings of histopathological evaluation also supported these observations (Ekundayo et al. 2022).

Gallic acid and donepezil

In a study, $AlCl_3$ significantly increased AChE activity in the brain as well as MDA & NO levels, while simultaneously decreasing total thiol level and the activities of SOD and CAT. These alterations were however reversed by donepezil only as well as combination of donepezil and gallic acid. Also, this combination significantly improved antioxidant status as opposed to donepezil alone. One could draw the conclusion that donepezil and gallic acid work in synergy, especially when it involves ameliorating the oxidative stress linked to $AlCl_3$-induced neurotoxicity (Obafemi et al. 2021).

Ginsenoside Rb1

Ginsenoside is abundantly found in Panax ginseng. In a recent study, ginsenoside Rb1 significantly attenuated the decrease in synaptophysin expression, the histopathological alterations in the cerebral cortex, the elevation of the expression of cleaved caspase-3, ionized calcium-binding adaptor molecule 1 (Iba-1), and glial fibrillary acidic protein (GFAP). Ginsenoside Rb1 may have a neuroprotective effect against $AlCl_3$–induced changes in the cerebral cortex by suppressing the formation of Aβ & phosphorylated tau protein, acting as an anti-apoptotic agent, minimizing gliosis, and correcting oxidative stress (Shalaby et al. 2023).

Ononin

Ononin, an isoflavone glycoside, is widely present in a variety of plants, including *Ononis angustissima*, *Smilax scobinicaulis*, & *Millettia nitida* (Li et al. 2014). Treatment with ononin successfully reduced behavioural alterations in AD animals caused by $AlCl_3$. In the brain tissues of AD animals, ononin also significantly reduced AChE, Aβ1-42, & MDA while increasing SOD and TAC. Also, the levels of IL-1β, TNF-α, p38MAPK, & NF-κB were reduced while BDNF and PPAR-γ contents were increased in AD animals. Ononin treatment may help to suppress the neuroinflammation and oxidative stress, & ameliorate the cognitive impairment found in the AD (Chen et al. 2021).

Asiatic acid

Asiatic acid is a key bioactive compound that offers *C. asiatica* (a medicinal plant) its antioxidative &

therapeutic effects (Nagoor Meeran et al. 2018). A recent study showed that $AlCl_3$ intoxication in rats results in severe memory impairment, increased anxiety-like behaviour, AChE activity, MDA level, and concurrently decreased SOD, & CAT activity in the cortex and hippocampus. $AlCl_3$-intoxication also accelerated neuronal loss and reactive astrogliosis in both regions. However, when Asiatic acid and $AlCl_3$ were administered together, the behavioral alterations were attenuated, SOD & CAT activities were restored, and AChE activity and MDA level were reduced. Asiatic acid also attenuated neuronal loss and reactive astrogliosis in rat brain (Suryavanshi et al. 2022).

p-Coumaric acid

p-Coumaric acid (p-CA) is a phenolic acid of the hydroxycinnamic acid family that can be found in many vegetables, fruits, and cereals, such as pears, apples, oranges, berries, grapes, potatoes, tomatoes, beans, onions, wheat, maize, and oats (Ferreira et al. 2019). p-CA has attracted a lot of interest recently due to its wide range of biological activities, such as antioxidant (Sakamula and Thong-Asa 2018), neuroprotective (Oh et al. 2021), anti-inflammatory (Yoon et al. 2014), & memory-improving effects (Daroi et al. 2022). p-CA can stimulate hippocampal synaptic plasticity (Lee et al. 2018) & promote hippocampal neurogenesis (He et al. 2021). p-CA has been explored for a variety of positive effects under different neuropathological alterations in both *in vitro* and *in vivo* studies (Li et al. 2019; Manyagasa and Thong 2019; Sakamula et al. 2019; He et al. 2021; Oh et al. 2021; Daroi et al. 2022). In a study, treatment with p-CA ameliorated hippocampal long-term potentiation (LTP) impairment, improved passive avoidance memory dysfunction, and hindered Aβ plaque accumulation in the hippocampal dentate gyrus of $AlCl_3$-treated rats (Rashno et al. 2022). These points to the possibility that p-CA may offer promising therapeutic potential to improve cognitive decline in neurodegenerative disease like AD (Rashno et al. 2022).

Naringin

Naringin is a citrus fruit flavonoid that may fight autophagic & oxidative stress in $AlCl_3$-induced AD. In a study, $AlCl_3$ caused memory impairment, but co-administration with naringin revealed a significant improvement. $AlCl_3$ also significantly increased lipid peroxidation and oxidative stress and decreased levels of reduced glutathione. Naringin administration however ameliorated these neurochemical alterations. $AlCl_3$ also caused an increase in the immunohistochemical expression of microtubule assembly (tau protein) and oxidative stress (iNOS), the decreased the expression of the autophagic marker (LC3) in the cerebellum. All these were ameliorated by naringin (Hassan et al. 2022).

Valeric acid

Valeric acid, a naturally occurring straight chain alkyl carboxylic acid found in *Valeriana officinalis* has been used to treat neurological diseases (Al-Attraqchi et al. 2020; Batista et al. 2023). Valeric acid treatment increased ACh levels in the hippocampus of AD rats. Valeric acid also significantly increased Gamma-Aminobutyric Acid (GABA), dopamine, glutamate, and serotonin levels, thereby reversing $AlCl_3$-induced impairment (Dulla et al. 2023). In another study, valeric acid treatment reduced the plasma level of Aβ1–42 biomarker and improved memory by reversing the $AlCl_3$–induced impairment (Dulla et al. 2021).

Baicalein

Baicalein, a flavonoid found in the roots of *Scutellaria lateriflora* & *Scutellaria baicalensis*, has a variety of biological functions, including anti-inflammatory & antioxidant (Ren et al. 2021), cardioprotective (Zhao et al. 2016), anticancer, & antiviral properties (Cathcart et al. 2016). It also possesses neuroprotective properties (Sowndhararajan et al. 2018) and inhibits AChE (Liao et al. 2022). In a study, the combination of baicalein and memantine significantly improved behavioural parameters. In addition to increasing BDNF expression, the combination reduced oxidative stress and Aβ plaques formation. Therefore, baicalein and memantine therapy may slow neurodegeneration progression in rats (Jadhav and Kulkarni 2023b).

Berberine

Many vegetable species including meadow rue (*Thalictrum*), barberry (Berberis), goldenseal (*Hydrastis canadensis L.*), celandine (*Chelidonium*), and *Phellodendron amurense*, contain berberine, a phytogenous alkaloid (Germán-Acacio et al. 2020). Berberine has been known to have therapeutic potential against AD. In AD rats, berberine significantly improved memory deficits, increased antioxidant enzyme levels, decreased AChE activity, lowered pro-inflammatory cytokines level, and significantly downregulated the expression of predefined biomarkers. Histological examination also showed that berberine can lower neuroinflammation & amyloid plaques in AD (Akash et al. 2023).

Curcumin

Curcumin found in curcuma has been studied for its antioxidant, anti-inflammatory, anticancer, & cytoprotective properties (Dhouib et al. 2017; Alhusaini et al. 2019; Abo-Zaid et al. 2020). In cellular and animal models of neurodegenerative disorders, curcumin was demonstrated to offer neuroprotection by upregulating the transcription of Nrf2 and suppressing the activation of NF-κB (Liao et al. 2012; Farkhondeh et al. 2021). A study found that curcumin administration increased the activities of antioxidant enzymes & the production of

anti-inflammatory cytokine, and decreases apoptotic cells in $AlCl_3$-indcued AD. Additionally, hippocampal histopathology examination showed that curcumin may be able to decrease the hallmarks in $AlCl_3$-induced AD (ELBini-Dhouib et al. 2021).

Sesamol

The anti-inflammatory activity of sesamol makes it a promising candidate to ameliorate neurotoxicity and neuroinflammation (Sachdeva et al. 2015; Castro-González et al. 2020). Sesamol can help with cognitive impairment and anxiety and has neuroprotective properties. Sesamol has been shown to prevent the accumulation of Aβ, alter the microbiota in the stomach, & improve the output of microbial metabolites (Yuan et al. 2019). Sesamol prevents neurotoxicity caused by Al via its antioxidant, anti-inflammatory, and anti-apoptotic effects (Abou-Zeid et al. 2021; Du et al. 2022). In an $AlCl_3$-intoxicated rat study, rats treated with a combination of sesamol and *Lactobacillus plantarum* (probiotic bacteria) showed markedly reduced levels of brain Aβ, p-tau, GSK-3β, apoptotic, and inflammatory biomarkers, as well as markedly elevated levels of brain free β-catenin and Wnt3a. Also, this combination significantly increased hepatic PPAR-γ expression while significantly reducing hepatic expressions of JAK-2/STAT-3, inflammatory (IL-6, TNF-α, NF-κB), fibrotic (MMP-2, TIMP-1, α-SMA) and apoptotic markers, (caspase-3), compared to $AlCl_3$-intoxicated rats. The effectiveness of this combination in halting the effect of neurotoxicity was supported by behavioural and histopathological evaluations (Abu-Elfotuh et al. 2023).

Silibinin

Silibinin (silybin) is abundantly found in silymarin. Silymarin is found in the fruits & seeds of *Silybum marianum* (Haddadi et al. 2020). $AlCl_3$-induced cognitive impairment, neurochemical anomalies, and histopathological alterations were significantly alleviated by treatment with silibinin-loaded nanostructured lipid carriers (Sili-NLCs) (Makhdoomi et al. 2022). This implies that Sili-NLCs could potentially act as a neuroprotective agent against AD, as treatment with Sili-NLCs is more effective than treatment with free silibinin in preventing the development of neurotoxicity caused by Al (Makhdoomi et al. 2022).

Isoimperatorin

Lemon and lime oils contain isoimperatorin, an active natural furanocoumarin (Lai et al. 2021). Isoimperatorin has anti-inflammatory effect as one of its pharmacological actions (Wijerathne et al. 2017; Chen et al. 2021). Isoimperatorin significantly reduced the effect of $AlCl_3$ in a mouse model of AD via the modulation of antioxidant system, and regulation of inflammatory response by targeting Nrf2 and MAPK (Rajendran et al. 2023). Therefore, isoimperatorin may be a potential therapeutic option for neurotoxicity and neurodegenerative diseases which are associated with neuro-inflammation and oxidative stress, such as AD.

Crocin

The primary and most potent active component in *Crocus sativus* is crocin, often known as saffron and a member of Iridaceae family. It has been established that crocin offer neuroprotective benefits. Crocin has a unique, prophylactic effect against ethanol-induced damage to learning and memory. A study found that crocin protected against $AlCl_3$–induced neurodegenerative behavioural and biochemical alterations. It alleviated $AlCl_3$-induced memory impairment, and reduced oxidative stress and cholinergic dysfunction. Thus, crocin may be a useful medication for the management of AD (Tomar et al. 2023).

Betulin

The Betulaceae family, especially *Betula alba*, *B. platyphylla*, *B. pubescens*, and *B. pendula* the richest source of betulin, a lupane-type compound that may be obtained from more than 200 plants species (Hordyjewska et al. 2019). A new drug that is effective in both the prevention and treatment of AD may be developed from betulin due to its neuroprotective properties. In one study, rats with $AlCl_3$-induced AD exhibited improved spatial memory and lowered levels of TNF-α, Aβ, and amyloid precursor- like protein 2 (APLP2) when administered betulin in complex with cyclodextrin (Zakrzeska et al. 2023).

Palmatine

Palmatine, a naturally occurring protoberberine alkaloid, is present in *Coptis chinesis* and *Corydalis yanhusuo*. In a study, treatment with palmatine significantly regulated the levels of AChE levels and glutamate, improved the expression of BDNF, and lowered excitotoxic damage and the expression of IL-6 and TNF-α, induced by Al. Additionally, palmatine prevented neuronal damage degeneration and loss and restored healthy, viable neurons in AD (Baburaj et al. 2023).

Malvidin

In animal cell line and *in vivo* models, malvidin, an anthocyanin derived from red wine, has been shown to offer protection against oxidative neuronal damage. It is used in the treatment of variety of ailments due to its antioxidant properties. Malvidin targets MAPK and NFκB pathways, these contribute to its antioxidant, anti-inflammatory, and anti-apoptotic actions (Hou et al. 2004). It has been demonstrated that malvidin reduced $AlCl_3$–induced behavioural impairment. Oral treatment of malvidin also demonstrated neuroprotective effects via the regulation of antioxidant levels and neuroinflammation and inhibition of AChE activity $AlCl_3$-exposed rats. Malvidin may therefore be a potential drug for the treatment of AD (Gilani et al. 2022).

Table 2. Neuroprotective and Therapeutic Effects of Natural Products against Aluminium Chloride-Induced Alzheimer's Disease.

Natural product	Dose of $AlCl_3$	Dose of natural product	Animals used	Mechanism of Action	Ref
Morin (MOR), Thymol (TML), and Thymoquinone (TMQ)	70 mg/kg i.p. daily for 5 weeks	20 mg/kg of MOR orally, TML (30 mg/kg), 10 mg/kg of TMQ, and PhM	Rats	Antioxidant, anti-inflammatory, anti-apoptotic, and improved learning & memory	(Hamdan et al. 2022)
Niruriflavone	100 mg/kg of $AlCl_3$ for 42 days.	0.125 mg/kg b.wt. from the 42^{nd} day to the 60^{th} day by oral route	Rats	Antioxidant, anticholinesterase, & reversed neurobehavioral changes	(Rajamanickam and SL 2022)
Quercetin	50 mg/kg for 28 days orally	25 or 50 mg/kg orally for 28 days after AD induction	Rats	Anti-Aβ, attenuated behavioural & neurotransmission impairments	(Elfiky et al. 2021)
Quercetin	50 mg/kg b.wt. i.p. for 60 days	50 mg/kg b.wt. by gastric intubation (1h prior to $AlCl_3$)	Rats	Modulated gene expression, & improved short-term memory	(Elreedy et al. 2023)
Resveratrol-tannic acid	100 mg/kg/day p.o. for 90 days	Resveratrol (20 mg/kg/day p.o.) and tannic acid (50 mg/kg/day p.o.)	Rats	Antioxidant, anti-Aβ, & attenuated cognitive impairment	(Bhounsule and Bhatt 2023)
Thymoquinone (TQ), & Celastrol	10 mg/ kg/day i.p. for 6 weeks	10mg/kg/day TQ i.p. & 1mg/kg/day celastrol i.p. for 6 weeks	Rats	Antioxidant, anti-inflammatory, modulated neurotransmitters levels, & improved cognitive impairments and brain BDNF expression	(Abbas et al. 2022)
Betalain	100 mg/kg b.wt. for 28 days orally	10 or 20 mg/kg b.wt. for 28 days (1hr prior to $AlCl_3$)	Rats	Antioxidant, anticholinesterase, anti-inflammatory, & suppressed learning impairments	(Shunan et al. 2021)
Quercetin + Memantine	100 mg/kg orally for 42 days	Memantine (20mg/kg), quercetin (50mg/kg), memantine & quercetin (20 + 25mg/kg), or memantine & quercetin (20 + 50mg/kg) orally for 42 days	Rats	Antioxidant, anti-Aβ, anticholinesterase, improved learning and memory, & BDNF expression	(Jadhav and Kulkarni 2023a)
Vinpocetine + Epigallocatechin-3-gallate	100 mg/kg b.wt. i.p for 4 weeks	Vinpocetine (20 mg/kg, p.o) + EGCG (10 mg/kg i.p) for 4 weeks	Rats	Antioxidant, anti-inflammatory, anticholinesterase, anti-Aβ, & regulated monoamines & BDNF levels	(Ali et al. 2022)
β-sitosterol	10 mg/kg for 14 days	25 mg/kg for 21 days	Mice	Antioxidant, anti-Aβ, & mitigated cognitive impairment	(Yadav et al. 2023)
Gallic acid or Hesperidin	100 mg/kg/day via oral gavage for 21 days	100 mg/kg gallic acid or 100 mg/kg hesperidin for 21 days	Rats	Antioxidant, anticholinesterase, anti-inflammatory, prevented cognitive impairment & improved neurotransmitters levels	(Ekundayo et al. 2022)

Table 2. *Cont.*

Natural product	Dose of $AlCl_3$	Dose of natural product	Animals used	Mechanism of Action	Ref
Gallic acid + donepezil	100 mg/kg via oral gavage for 60 days	10 mg/kg Donepezil + 50 mg/kg Gallic acid via oral gavage for 60 days	Rats	Antioxidant, & anticholinesterase	(Obafemi et al. 2021)
Ginsenoside Rb1	50 mg/kg/day s.c. for 8 weeks	70 mg/kg/day orally for 8 weeks (1hr before $AlCl_3$)	Mice	Antioxidant, anti-apoptotic, anti-Aβ, improved memory impairment, mitigated accumulation of phosphorylated tau protein, & attenuated histopathological changes.	(Shalaby et al. 2023)
Ononin	175 mg/kg orally for 25 days	30 mg/kg orally from the 25th day to 36th day (after $AlCl_3$ for 25 days)	Rats	Alleviated cognitive impairment, antioxidant, anti-neuroinflammatory, & restored brain histological structure.	(Chen et al. 2021)
Asiatic acid	100 mg/kg b.wt. orally for 8 weeks	75 mg/kg b.wt. orally for 8 weeks	Rats	Antioxidant, anticholinesterase, mitigated neuronal loss, & attenuated reactive astrogliosis	(Suryavanshi et al. 2022)
p-Coumaric acid	100 mg/kg/day p.o.	100 mg/kg/day p.o. (1hr prior to $AlCl_3$ administration)	Rats	Improved memory impairment, alleviated LTP impairment, & anti-Aβ	(Rashno et al. 2022)
Naringin	100 mg/kg/day p.o. for 21 days	100 mg/kg/day p.o. for 21 days	Rats	Behavioural, neurochemical, immunohistochemical, and molecular modulation	(Hassan et al. 2022)
Valeric acid	100 mg/kg b.wt. orally for 42 days	50 mg/kg b.wt. orally on the 47th day for 30 days	Rats	Regulated neurotransmitters level	(Dulla et al. 2023)
Baicalein + Memantine	100 mg/kg for 42 days	Memantine (20 mg/kg), Baicalein (10 mg/kg), memantine & baicalein (20 + 5mg/kg), or memantine & baicalein (20 + 10mg/kg) orally for 42 days	Rats	Behavioural improvement, antioxidant, anti-Aβ, & increased BDNF	(Jadhav and Kulkarni 2023b)
Berberine	300 mg/kg orally for 21 days	50mg/kg of berberine-enriched extract & 50 mg/kg of pure berberine orally for 21 days	Rats	Improved memory, antioxidant, anti-inflammatory, anticholinesterase	(Akash et al. 2023)
Valeric acid	100 mg/kg b.wt. for 42 days orally	50 mg/kg b.wt. for 30 days after 42 days of $AlCl_3$ administration		Memory improvement, anti-Aβ	(Dulla et al. 2021)
Resveratrol-Selenium Nanoparticles	100 mg/kg/day for 60 days	200 mg/kg/day via gavage for 8 weeks	Rats	Antioxidant, anti-inflammatory, anti-Aβ, and improved cholinergic deficits	Abozaid et al. 2022

Table 2. *Cont.*

Natural product	Dose of $AlCl_3$	Dose of natural product	Animals used	Mechanism of Action	Ref
Resveratrol-Selenium Nanoparticles	300 mg/kg/day orally for 30 days	200 mg/kg for 3 weeks after $AlCl_3$ administration for 30 days	Rats	Antioxidant, and modulated neurotransmitter level	(AboZaid et al. 2021)
Curcumin	100 mg/kg b.wt. via oral gavage	100 mg/kg b.wt. via oral gavage	Rats	Improved behavioral impairments, antioxidant, and anti-inflammation	(ELBini-Dhouib et al. 2021)
Sesamol	70 mg/kg/day i.p. for 5 weeks	Sesamol (50mg/kg/day p.o.) *L. plantarum* (1×10^6 CFU/day p.o.) for 5 weeks	Rats	Prevented cognitive dysfunction, anti-inflammatory, anti-apoptotic	(Abu-Elfotuh et al. 2023)
Silibinin	100 mg/kg/day p.o.	50, 100, or 200 mg/kg/day p.o. for 30 days	Mice	Antioxidant, ameliorated cognitive impairments and histological changes	(Makhdoomi et al. 2022)
Quercetin nanoemulsion	100 mg/kg b.wt./day orally for 30 days	15 mg/kg b.wt./day i.p. for 30 days	Rats	Antioxidant, anti-inflammatory, modulated neurotransmitters, and mended histopathological changes	(Alaqeel et al. 2022)
Isoimperatorin	10 mg/wt/day orally	30 mg/wt/day i.p	Mice	Antioxidant, anti-inflammatory, and modulated behavioural and neurotransmitters deficit	(Rajendran et al. 2023)
Crocin	100 mg/kg orally for 42 days	15 or 30 mg/kg orally for 42 days	Rats	Antioxidant, anticholinesterase, and improved memory impairment	(Tomar et al. 2023)
Betulin	200 mg/kg/day	100 mg/kg/day, intragastrically during the last 50% of the experimental days	Rats	Improved spatial memory, anti-inflammatory, & anti-Aβ	(Zakrzeska et al. 2023)
Palmatine	100 mg/kg p.o. for 42 days	10 or 20 mg/kg p.o. for 42 days	Rats	Anticholinesterase, anti-inflammatory, lowered excitotoxic damage, & improved BDNF	(Baburaj et al. 2023)
Malvidin	50mg/kg b.wt./day i.p. for 60 days	100 or 200 mg/kg p.o. (1hr prior to $AlCl_3$ injection) for 60 days	Rats	Antioxidant, anti-inflammatory, anticholinesterase, & downregulated memory impairment.	(Gilani et al. 2022)

Note: $AlCl_3$: Aluminium Chloride; Aβ: Amyloid-beta; AD: Alzheimer's disease; BDNF: Brain-derived neurotrophic factor b.wt.: body weight; i.p.: intraperitoneally; p.o.: Oral administration; s.c.: subcutaneous

CONCLUSIONS

A growing body of evidence suggests that exposure to $AlCl_3$ and its neurotoxicity may play a role in a variety of neurodevelopmental & neurodegenerative disorders. $AlCl_3$ neurotoxicity has been linked to oxidative stress, mitochondrial dysfunction, inflammation, accumulation of Aβ plaques and NFT, & alteration of synaptic plasticity and signal transduction due to interference with neurotransmitter systems. Treatment of $AlCl_3$ neurotoxicity and associated diseases like AD may benefit from targeting these mechanisms at different stages.

Mechanistic studies are currently being conducted to validate and promote the use of traditional medicines in animal models. The majority of the medicinal plants and natural products discussed in this review have been shown to have neuroprotective, antioxidant, anti-

amyloid, anti-inflammatory, anticholinesterase, anti-apoptotic, and therapeutic actions. Nevertheless, the majority of the plant herbs have not yet been isolated, and further research on these natural products needs to be conducted, which is an intriguing feature in the treatment of AD.

All currently available drugs of AD are utilized to treat the symptoms of the disease. Hence, there is an urgent need for the development of new drugs with novel targets that can also prevent the progression of the disease at an early stage, thereby improving the quality of life of AD patients. The insight in this review will undoubtedly help researchers to design compounds that have a significant impact in curing AD.

Recommendation

A promising path for AD care is the identification of preventive medicines derived from conventional herbal medication. It is likely to be beneficial to screen herbal medicine for lead compounds based on their physicochemical characteristics and projected BBB properties in order to discover new treatment for AD. Future research can focus more on natural compounds that can cross the BBB, have wide therapeutic time windows, clear pharmacological goals, & fewer side effects.

However, it is challenging to trace the pharmacological effects of a plant or plant extract to a single component or class of chemicals since the purported protective and therapeutic characteristics of herbal medicine are typically the result of the synergistic actions of several compounds. There are also critical factors to take into account, like interactions with already-available drugs.

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