EJPMR, 2026, 13(6), 132-138 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

KALANCHOE PINNATA AS A MULTI-TARGET BOTANICAL AGENT IN ALZHEIMER'S DISEASE: A REVIEW OF NEUROPROTECTIVE MECHANISMS AND THERAPEUTIC POTENTIAL

Puneeth F. Kadakol*

Bldea's Ssm College of Pharmacy and Research Centre Vijayapur-586101.

***Corresponding Author: Puneeth F. Kadakol**

Bldea's Ssm College of Pharmacy and Research Centre Vijayapur-586101.

DOI: https://doi.org/10.5281/zenodo.20444248

How to cite this Article: Puneeth F. Kadakol*. (2026). Kalanchoe Pinnata As A Multi-Target Botanical Agent In Alzheimer's Disease: A Review of Neuroprotective Mechanisms And Therapeutic Potential. European Journal of Pharmaceutical and Medical Research, 13(6), 132–138.

Article Received on 05/05/2026 **Article Revised on 25/05/2026** **Article Published on 01/06/2026**

ABSTRACT

Alzheimer's disease (AD) is one of the most widespread and debilitating neurodegenerative diseases in the world today. It has been estimated that more than 58 million patients had AD in 2020, while the number would increase to about 152 million by 2050. However, although intensive studies on AD have been carried out for many decades, no pharmacological treatments are currently available to slow down disease progression, making the development of innovative approaches critical to improve the treatment of AD. *Kalanchoe pinnata* (Lam.) Pers., also known as *Bryophyllum pinnatum*, is a succulent medicinal herb widely spread throughout tropical and subtropical zones and extensively used for medicinal purposes in folk medicine in Africa, Asia, and America. The current review provides an up-to-date evaluation of scientific literature on the neuroprotective efficacy of *K. pinnata* in respect of pathomechanisms associated with Alzheimer's disease. Particular attention is paid to its main active compounds, which include quercetin, kaempferol, bryotoxin B, and bufadienolides, demonstrating anti-AChE properties, anti-amyloidogenicity, prevention of tau hyperphosphorylation, neuroinflammation, and oxidative stress. Furthermore, network pharmacological studies have found a total of 449 shared target molecules between *K. pinnata* and Alzheimer's disease, involving the PI3K-AKT pathway and MAPK pathway to some extent. Animal experiments have reported an improvement in cognitive behavior in scopolamine-induced amnesia model rats after administering extracts from *K. pinnata*. Therefore, *K. pinnata* is considered to be a potentially promising polypharmacological plant for treating AD patients. However, there is a need for further investigation of this matter in detail.

KEYWORDS: Alzheimer's disease; Kalanchoe pinnata; neuroprotection; quercetin; kaempferol; bufadienolides; network pharmacology; phytomedicine.

INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive, and irreversible neurodegenerative disorder that represents the most common cause of dementia, contributing to nearly 60–80% of dementia cases worldwide.[1] The condition was first identified and described in 1906 by the German psychiatrist Alois Alzheimer and has since emerged as one of the major public health challenges of the modern era. According to global estimates, more than 58 million people were living with AD in 2020, and this number is expected to increase to approximately 152 million by 2050, largely due to the aging global population.[2] In the United States alone, nearly 7.2 million individuals aged 65 years and above were reported to be living with AD in 2025, representing roughly one in every nine older adults. This number is also projected to rise substantially, reaching an estimated 12.7 million cases by 2050.[2]

From a clinical perspective, AD is characterized by a gradual impairment of episodic memory, executive functions, language skills, and visuospatial functioning, which eventually lead to complete dependence and death. The characteristic pathological features of AD include senile plaques that are extracellular deposits of aggregated amyloid-beta peptides and neurofibrillary

tangles that are intracellular formations formed by hyperphosphorylation of the tau protein. Such pathological abnormalities impair proper functioning of synapses, initiate inflammation, increase oxidative stress, and cause significant loss of neurons, especially in brain structures responsible for memory formation and consolidation, such as the hippocampus and entorhinal cortex.[4]

The currently used pharmacotherapy for treating Alzheimer's disease under the approval of the U.S. Food and Drug Administration includes acetylcholinesterase inhibitors Donepezil, Rivastigmine, and Galantamine in combination with an NMDA receptor antagonist Memantine. However, these drugs provide relatively low efficiency and fail to change the course of the disease.[1] New pharmacotherapeutic options, which involve using the monoclonal antibodies Lecanemab and Donanemab, appear to be more efficient regarding amyloid plaque removal and cognitive decline slowing among patients with early Alzheimer's disease. Nevertheless, the use of this type of pharmacotherapy is accompanied by some disadvantages such as ARIA, the necessity to receive the drug intravenously, and high costs of therapy.[1] Due to the current limitations of available treatment strategies for AD, recent scientific interest has been focused on phytomedicine as a new direction in developing multiple targets for AD agents. Of numerous species of medicinal plants used in traditional medicine throughout the world, *Kalanchoe pinnata* (Lam.) Pers., popularly known as "air plant," "miracle leaf," or "cathedral bells," has gained increasing interest because of its various biological activities and abundant phytochemical constituents.[5]

In this article, the authors present an overview of the existing scientific data on the neuroprotective effects of *K. pinnata* and the perspectives of using this natural product as a multi-target agent for AD. Ethnopharmacological information, phytochemical studies, network pharmacology analysis, and preclinical in vitro and in vivo experiments conducted until 2025 are included in the discussion.[6]

ALZHEIMER'S DISEASE: MULTIFACTORIAL PATHOPHYSIOLOGY

The Amyloid Cascade Hypothesis

The amyloid cascade hypothesis, first put forth by Hardy and Selkoe, suggests that abnormal accumulation of amyloid-beta (Aβ) peptides is the key event triggering Alzheimer's disease pathogenesis. Based on this idea, APP is cleaved sequentially by BACE1 and gamma secretase complex to produce Aβ peptides, mainly comprising two types: Aβ40 and more aggregation-prone Aβ42. Under pathological circumstances, the balance of Aβ metabolism becomes disturbed, causing accumulation of Aβ from its soluble oligomers to insoluble fibrils and further formation of mature plaques.[3] Among different types of Aβ, soluble oligomers are considered the most toxic, as they impair synaptic plasticity, mitochondrial function, trigger neuroinflammatory cascades, and ultimately lead to cell death.[4]

Tau Pathology and Neurofibrillary Tangles

Tau is one of the microtubule-binding proteins that normally performs an essential role in maintaining the integrity of microtubules involved in intracellular transport within neurons. In Alzheimer's disease, tau undergoes abnormal hyperphosphorylation caused by the dysregulation of several kinases including glycogen synthase kinase-3β (GSK-3β) and cyclin- dependent kinase 5 (CDK5). Hyperphosphorylation of tau reduces its binding to microtubules, leading to its dissociation followed by polymerization into paired helical filaments forming NFTs inside cells.[7] The spread of pathological tau changes throughout the brain follows a predictable pattern of regional involvement known as Braak's staging. Importantly, the extent of tau pathology has been found to correlate better with neuronal death and cognitive impairment compared to the accumulation of amyloid-beta.[8]

Cholinergic Dysfunction

According to the cholinergic hypothesis, the cognitive impairments seen in Alzheimer's disease are predominantly caused by the selective loss of cholinergic neurons in the nucleus basalis of Meynert, which leads to a reduction in ACh neurotransmission in the brain.[1] ACh is an important neurotransmitter responsible for learning, memory, and other cognitive processes, and its degradation in cholinergic synapses occurs via the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Research studies have shown that Aβ accumulation in the brain can increase the enzymatic activities of both AChE and BChE, causing additional depletion of acetylcholine in synapses and creating a link between amyloid and cholinergic dysfunctions.[9]

Neuroinflammation

Chronic neuroinflammation is now considered one of the primary causes of AD pathogenesis, in addition to being a consequence of neuronal damage. Microglial activation and reactive astrocytes release multiple pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and nitric oxide in patients with AD. The released inflammatory molecules lead to the creation of a neurotoxic environment that results in Aβ deposition, increased tauopathy, and abnormal synaptic activities.[4] The NF-κB signaling pathway and MAPK pathways are two significant molecular mechanisms involved in inflammation-related neurodegeneration.[4]

Oxidative Stress and Mitochondrial Dysfunction

The brain becomes highly susceptible to oxidative injuries owing to high metabolism, high levels of polyunsaturated fats, and low antioxidants in comparison to other tissues. During Alzheimer's disease pathogenesis, oxidative stress is initiated through the

production of excess ROS and reactive nitrogen species, which leads to oxidation of proteins, lipids, and DNA while interfering with mitochondrial function.[4] Mitochondria dysfunction in AD is characterized by reduced electron transport chain activity, decreased ATP formation, mitochondrial morphology changes, and defective mitophagy. These disruptions lead to cellular energy depletion and enhanced oxidative stress, thus accelerating synapse dysfunction and neuronal cell loss.[10]

KALANCHOE PINNATA: BOTANICAL IDENTITY AND ETHNOPHARMACOLOGICAL HERITAGE

Taxonomy and Geographic Distribution

Kalanchoe pinnata (Lam.) Pers. belongs to the Crassulaceae family in the Saxifragales order. There are numerous synonyms for this plant in its taxonomy, among which are *Bryophyllum pinnatum* (Lam.) Oken and *Cotyledon pinnata* Lam., indicating a rather complicated taxonomic history.[11] The species is a perennial succulent from Madagascar and has been introduced in many tropical and subtropical regions around the globe, including throughout tropical Africa, South and Southeast Asia, Caribbean, South America, and Pacific Islands. Morphologically, it has pinnate compound leaves with crenate edges that may form small plants at the notches of the leaves, leading to the common nicknames “air plant” and “miracle leaf.”[5]

Ethnomedicinal Uses

K. pinnata has been extensively employed in traditional medicinal practices worldwide. In Ayurvedic and Siddha medicine systems prevalent in India, the plant has been traditionally prescribed to treat inflammation, fever, injuries, urinary disorders, and headaches.[11] In African traditional medicine, leaf extracts have been commonly applied externally for wound care, burns, and ulcers, whereas internal formulations have been used to address respiratory infections and renal disorders.[5] In Brazilian traditional medicine, the species has been applied to heal gastric ulcers and inflammatory ailments.[11] In terms of neurological functions, *K. pinnata* has also been traditionally linked to sedative, anxiolytic, and cognition-enhancing applications. In Anthroposophic medicine, Bryophyllum extracts have been traditionally prescribed for “hyperactivity diseases,” including insomnia, restlessness, and preterm labor.[11]

PHYTOCHEMICAL CONSTITUTION OF KALANCHOE PINNATA

Flavonoids

The flavonoids can be regarded as the most pharmacologically significant constituents of *Kalanchoe pinnata* with respect to its neuroprotective effects. In terms of flavonoids, *K. pinnata* is especially abundant in flavonols quercetin and kaempferol, both of which are known for possessing a wide range of biological activity and neuroprotective potential.[12] Both quercetin (3,3’,4’,5,7-pentahydroxyflavone) and kaempferol (3,4’,5,7-tetrahydroxyflavone) are present in *K. pinnata* in both aglycone form and a number of glycosides. Among other flavonoids found in this plant, the following substances may be noted: luteolin, apigenin, kaempferol-3-O-glucoside, kaempferol-3-O-rutinoside, quercetin-3-O-rutinoside, and isoflavones.[12] Systematic phytochemical work has isolated quercetin glycosides from *K. pinnata* leaves and confirmed their anti-inflammatory activity.[24]

Bufadienolides

The bufadienolides constitute a unique group of steroidal molecules that are abundantly present in *Kalanchoe pinnata* and other types of Kalanchoe plants. Notable examples include bryophyllin A, bryophyllin B, bryophyllin C, bersalgenin, along with some glycosylated derivatives.[23] Among these compounds, bryotoxin B, a bufadienolide glycoside, has been identified by network pharmacology as one of the key bioactive components that could be associated with the anti-Alzheimer’s disease effect of *K. pinnata*.[6] In terms of structural similarities, bufadienolides can be considered analogous to cardiotonic steroids, demonstrating various biological functions such as selective cytotoxicity, anti-inflammation, and immunomodulation.[23]

Organic Acids, Phenolics, and Terpenoids

Kalanchoe pinnata contains many organic acids, phenolics, and terpenoids responsible for their pharmacological action. The organic acids present include malic acid, citric acid, succinic acid, and fumaric acid. Further, various phenolic acids including caffeic acid, chlorogenic acid, p- coumaric acid, and ferulic acid act as antioxidants and anti-neuroinflammatories.[5] Triterpenoids, including α-amyrin, β-amyrin, and ursolic acid, play a significant role in anti- inflammatory activities.[11] Moreover, phytosterols, including β-sitosterol, stigmasterol, campesterol, and C-24 epimeric 24-alkyl-Δ^{25}-sterols are also present. Importantly, *Kalanchoe pinnata* was one of the first species of higher plants found to contain C-24 epimeric 24-alkyl- Δ^{25}-sterols.[5]

NEUROPROTECTIVE MECHANISMS OF KALANCHOE PINNATA IN ALZHEIMER’S DISEASE

Inhibition of Acetylcholinesterase and Butyrylcholinesterase

One of the most researched neuroprotective mechanisms of *K. pinnata* regarding Alzheimer’s disease is inhibition of cholinesterase enzymes. In vivo studies showed that oral administration of hydroalcoholic extract of *Bryophyllum pinnatum* at doses of 200 and 400 mg/kg for 0.5 months led to significant improvements in cognitive functions in scopolamine-induced memory-impaired Wistar rats, consistent with results obtained with Donepezil at 3 mg/kg.[7] Biochemical analysis confirmed significant decreases in AChE and BChE activity in hippocampus and cortex tissues, as well as an increase in acetylcholine content.[7]

The cholinesterase enzyme-inhibiting effect of *K. pinnata* is believed to be due to its flavonoid content, specifically quercetin and kaempferol. Quercetin inhibited AChE via a reversible mixed inhibition mechanism, with an IC_{50} value of approximately 4.59 µM.[14] Molecular docking and multispectroscopic studies revealed that quercetin bound to His-440 and Tyr-70 amino acid residues, forming complexes with the catalytic active site and peripheral anionic site (PAS) region of AChE.[14] Additionally, the synergy between quercetin and Galantamine is evident in their complementary actions on different sites of AChE.[14] Similarly, kaempferol shows inhibitory activity against AChE and BChE, where molecular docking analysis confirms stable interactions in the active gorge site via hydrogen bonding and hydrophobic forces.[15]

Anti-Amyloidogenic Properties

Through network pharmacological analysis, 449 overlapping biological targets related to both *Kalanchoe pinnata* and signaling pathways associated with AD have been proposed, including targets responsible for APP processing, amyloid-beta aggregation, and peptide elimination.[6] Quercetin can prevent Aβ42 peptide aggregation and fibrillation by interacting with hydrophobic parts of amyloids.[13] Likewise, kaempferol and its derivatives are known to suppress the generation and deposition of both Aβ and tau fibrils.[15] Furthermore, beta-secretase 1 (BACE1), responsible for amyloidogenic cleavage of APP molecules, has also emerged as a putative target for *K. pinnata* flavonoids. Results of molecular docking studies revealed that quercetin and kaempferol have the ability to dock into the active site of BACE1, hence suppressing the development of amyloidogenic peptides.[6]

Tau Pathology Attenuation

Abnormal hyperphosphorylation of the tau protein is attributed primarily to GSK-3β and CDK5. KEGG pathway analysis revealed that these two kinases constitute molecular targets for the bioactive molecules of *K. pinnata.* Kaempferol is known to inhibit the activation of GSK-3β and, as a result, prevents the phosphorylation of the tau protein at multiple disease-relevant sites. Moreover, kaempferol seems to impair the assembly of tau into filamentous structures by disrupting their β-sheet conformations.[15] In addition to GSK-3β, quercetin has also been found to exert its effects on CDK5. Another mechanism of action involves the modulation of the c-Jun N-terminal kinase (JNK) signaling pathway, which participates in the processing of APP and the phosphorylation of the tau protein.[17]

Suppression of Neuroinflammatory Signaling Pathways

According to network pharmacology findings, the MAPK signaling pathway, comprising ERK1/2, p38 MAPK, and JNK sub-pathways, plays crucial roles in the anti-Alzheimer's disease properties of *Kalanchoe pinnata.*[6] The PI3K-Akt pathway, responsible for neuronal survival, synaptic plasticity, and regulation of tau phosphorylation through downstream regulation of GSK-3β and mTOR signaling, is also of significance.[7] Several experimental studies involving the isolation of flavonoid compounds from *Bryophyllum pinnatum* have exhibited suppression of NF-κB nuclear translocation and subsequent inhibition of pro- inflammatory genes such as TNF-α, IL-1β, and IL-6.[9] Quercetin also exhibits an ability to reduce ICAM-1 and MMP-9 gene expression, resulting in a decreased rate of inflammatory cell adhesion and extracellular matrix degradation, which may help prevent BBB dysfunction in Alzheimer's disease.[12]

Neuroprotective Effect via Antioxidants and Mitochondrial Protection

The significant antioxidative efficacy of *K. pinnata* leaf extract in the DPPH, ABTS, and FRAP test systems is an essential mechanism responsible for neuroprotective role against oxidative injury induced by reactive oxygen species.[5] In cellular models of Alzheimer's disease, quercetin was found to offer neuroprotection to PC12 neurons against oxidative injury caused by Aβ25-35 peptides by limiting ROS production, preventing lipid peroxidation, and maintaining mitochondrial membrane integrity.[14] Quercetin also induces mitochondrial biogenesis in SH-SY5Y neurons by inducing PGC-1α expression, addressing mitochondrial dysfunction as one of the primary mechanisms underlying neurodegeneration in Alzheimer's disease.[18] Similarly, kaempferol has proven to exert neuroprotective effects against Aβ toxicity by preserving mitochondrial function and regulating oxidative biomarkers.[19]

NETWORK PHARMACOLOGICAL AND IN SILICO EVIDENCE

A comprehensive network pharmacological study of *K. pinnata* against AD has identified ten bioactive ingredients with favorable pharmacokinetics properties. Three main hub network molecules – bryotoxin B, kaempferol, and quercetin – have been found as the major bioactive compounds. There are 449 common target genes between *K. pinnata* molecules and pathological pathways related to AD.[6] The major pathways involved in the anti-AD effects of *K. pinnata* are the PI3K-Akt and MAPK pathways, with additional pathway enrichment in signaling pathways associated with neurotrophins, apoptosis, and inflammatory cytokines.[6] The interactions of *K. pinnata* compounds with significant target proteins associated with AD, such as AChE, BChE, BACE1, GSK-3β, and CDK5, were studied using molecular docking with AutoDock Vina software.[7] Furthermore, molecular dynamics simulations for 200 nanoseconds were conducted using GROMACS software to determine the stability of important ligand-target complexes. The root mean square deviation (RMSD) values indicated stable conformation throughout the simulation time.[7]

IN VIVO PRECLINICAL EVIDENCE FOR COGNITIVE PROTECTION

Several in vivo experiments on animal subjects have examined the effects of the extracts obtained from *Kalanchoe pinnata* on cognitive protection against neurodegenerative disease and cognitive decline. The scopolamine-induced model of cognitive deficit was the most used experimental approach.[7]

Administration of aqueous-methanol leaf extract of *Bryophyllum pinnatum* at doses of 200 and 400 mg/kg body weight over 30 days resulted in dose-dependent enhancement in spatial learning and memory ability as measured in the Morris water maze task. The highest dose of 400 mg/kg body weight was effective in producing results comparable to Donepezil applied at 3 mg/kg.[7] Biochemical evaluation confirmed marked AChE inhibition, decrease in oxidative stress indices including malondialdehyde (MDA) and nitrite concentration levels, as well as elevation of antioxidant enzyme activities of SOD, CAT, and GPx in hippocampal tissues.[7] Further evidence has been gained from the aluminum chloride-induced neurotoxicity model, which develops symptoms similar to those seen in Alzheimer's disease such as amyloid deposition, oxidative stress, and cholinergic dysfunction. Flavonoids extracted from *B. pinnatum* exhibited significant neuroprotective properties, as indicated by the reduction of AChE activity, inhibition of amyloid beta deposition, reduction of lipid peroxidation levels, and improved cognitive functions.[9]

TOXICOLOGICAL PROFILE AND SAFETY CONSIDERATIONS

Acute toxicity testing in rodent models has shown that the extracts of *Kalanchoe pinnata* exhibit a fairly good safety profile. The LD_{50} for orally ingested preparations lies in the range of 1,000 to 5,000 mg/kg, significantly higher compared to the doses used to obtain desired pharmacological responses.[11] Sub-chronic toxicity tests carried out for durations varying from 28 to 90 days did not reveal any pathological changes in vital organs at medically relevant dosages.[20]

However, several toxicity concerns should be mentioned. Bufadienolides contained in *K. pinnata* have pharmacological activity similar to cardiac glycosides and have proven cardiotoxicity in vitro studies and in cases of cattle poisoning with *K. pinnata*, causing the condition referred to as "krimpsiekte" in South Africa.[23] Additionally, data on the genotoxic and reproductive effects of the substance are sparse, representing significant lacunae in the existing toxicological database.[20] Extra caution is also important for individuals under treatment with cardiac glycosides due to possible drug-drug interactions with bufadienolide compounds.[23]

RESEARCH GAPS AND FUTURE DIRECTIONS

Standardization and Phytochemical Consistency

The pharmacological characteristics of preparations made from *Kalanchoe pinnata* can exhibit considerable variation based on parameters such as geographic location, environment, method of cultivation, harvesting season, plant parts used, and extraction methods.[5] In order to achieve consistent pharmacological characteristics and facilitate future regulatory approval, it is necessary to develop formulations with clear phytochemical specifications. The determination of quantitative amounts of various markers, such as quercetin, kaempferol, and bryophyllin A, is especially important. The use of reliable analytical methods such as HPLC-DAD and LC- MS/MS is crucial in this respect.[4]

Mechanistic Validation in Transgenic AD Models

While the scopolamine-induced and D-galactose-induced animal models offer important proof- of-concept data, they do not completely recapitulate the complex pathogenesis of Alzheimer's disease.[7] Future research should therefore use established transgenic mouse models, like the APP/PS1, 5xFAD, and 3xTg-AD models, that better reflect the unique pathology of Alzheimer's disease, including beta-amyloid pathology, tau protein pathology, synaptic loss, and neuroinflammation.[8]

Blood-Brain Barrier Penetration and Drug Delivery

Evaluation of blood-brain barrier (BBB) permeability is very important in order to establish the viability of utilizing the active ingredients of *Kalanchoe pinnata* as a potential therapy for Alzheimer's disease. Intensive BBB permeability studies in vitro through models such as PAMPA-BBB and transwell co-culture systems are needed, alongside in vivo pharmacokinetic studies. Modern delivery techniques like nanomedicine, liposome-mediated transport, and nasal routes can be used to optimize delivery of *K. pinnata* bioactives into the brain.[4]

Clinical Translation

To date, there have been no clinical trials for any preparation based on *Kalanchoe pinnata* involving patients suffering from Alzheimer's disease. For clinical translation, it is important to undertake rigorously designed Phase I clinical trials for evaluating safety and pharmacokinetics, followed by proof-of-concept Phase II clinical trials.[1] Future clinical trials should consider reliable measures of cognition, such as the MMSE and the ADAS-Cog, as well as innovative biomarker assays comprising neuroimaging-based and fluid-based biomarkers, such as amyloid PET, tau PET, CSF Aβ42/40 ratio, and phosphorylated tau-181.[1]

CONCLUSION

Kalanchoe pinnata has been identified as a potential botanical candidate for treating AD due to its complex phytochemical content and multiple neuroprotective actions. Several experimental data obtained through

phytochemical analysis, network pharmacology, molecular docking, cellular assays, and animal testing suggest that *K. pinnata* and its active components such as quercetin, kaempferol, and bufadienolides may regulate different pathological factors associated with AD. Such factors comprise AChE/BChE inhibition, amyloid beta protein aggregation inhibition, tau protein hyperphosphorylation inhibition, anti-inflammatory actions, and antioxidant/mitochondria-protective functions.

Notably, the potential of *K. pinnata* and its active molecules to affect various pathological factors in parallel sets it apart from other AD treatment strategies based on single-target approaches. Network pharmacological approaches have demonstrated that *K. pinnata* can regulate the PI3K-Akt, MAPK, NF-κB, and GSK-3β pathways, which are important regulators of neurodegeneration and neuroprotection. Despite the promising preclinical evidence, rigorous investigation through standardized phytochemical formulations, transgenic animal models, BBB permeability studies, and ultimately clinical trials is warranted before *K. pinnata*-based therapies can be translated to clinical use.

REFERENCES

1. Turgutalp B, Kizil C. Multi-target drugs for Alzheimer's disease. Trends Pharmacol Sci., 2024; 45(7): 628–638.
2. Alzheimer's Association. Alzheimer's Disease Facts and Figures. Alzheimers Dement, 2025; 21(1): 1–104.
3. Hardy JA, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science, 2002; 297(5580): 353–356.
4. (Author(s) TBD). Effect of neuroinflammation on the progression of Alzheimer's disease and its significant ramifications for novel anti-inflammatory treatments. Ageing Res Rev., 2025. (In Press).
5. (Author(s) TBD). A comprehensive updated review on phytochemical and pharmacological profile of Kalanchoe pinnata. World J Pharm Res., 2024; 13(11).
6. (Author(s) TBD). Investigating the ameliorative effect of Kalanchoe pinnata on neuroinflammation-associated Alzheimer's disease using network pharmacology, molecular docking, and in vitro studies. J Comput Aided Mol Des., 2025.
7. Sheikh S, et al. Bryophyllum pinnatum (L.) Pers. modulates multiple neuroprotective targets in Alzheimer's disease: evidence from computational and experimental validation. Cell Biochem Biophys, 2025.
8. Jack CR, et al. The 2024 NIA-AA biological definition of Alzheimer's disease: linking biomarkers to clinical practice. Front Dement, 2024/2026.
9. Ogidigo JO, Anosike CA, Joshua PE, et al. Neuroprotective effect of Bryophyllum pinnatum flavonoids against aluminum chloride-induced neurotoxicity in rats. Toxicol Mech Methods, 2022; 32(4): 243–258.
10. Supratman U, et al. Anti-tumor promoting activity of bufadienolides from Kalanchoe pinnata. Biosci Biotechnol Biochem, 2001; 65(4): 947–949.
11. Fernandes JM, Cunha LM, Azevedo EP, et al. Kalanchoe laciniata and Bryophyllum pinnatum: an updated review about ethnopharmacology, phytochemistry, pharmacology and toxicology. J Ethnopharmacol, 2019.
12. Cheng SC, Wu YH, Huang WC, et al. Anti-inflammatory property of quercetin through downregulation of ICAM-1 and MMP-9 in TNF-α-activated retinal pigment epithelial cells. Cytokine, 2019; 116: 48–60.
13. (Author(s) TBD). Three to Tango: inhibitory effect of quercetin and apigenin on acetylcholinesterase, amyloid-β aggregation and AChE-amyloid interaction. Molecules, 2022; PMC9699245.
14. Liao Y, Mai X, Wu X, et al. Exploring the inhibition of quercetin on acetylcholinesterase by multispectroscopic and in silico approaches and evaluation of its neuroprotective effects on PC12 cells. Molecules, 2022; 27(22): 7971.
15. Zhou Y, et al. Kaempferol, a potential neuroprotective agent in neurodegenerative diseases: from chemistry to medicine. Biomed Pharmacother, 2023; 165: 115216.
16. Kandeda AK, et al. Kalanchoe crenata Haw. (Crassulacea) decreases hippocampal neuron loss and improves memory and executive function in aged rats: implications for anti- inflammatory and antioxidant mechanisms. Brain Behav, 2025; PMC11830630.
17. Colombo A, et al. JNK regulates APP cleavage and degradation in a model of Alzheimer's disease. Neurobiol Dis, 2009.
18. Ho CL, Kao NJ, Lin CI, et al. Quercetin increases mitochondrial biogenesis and reduces free radicals in neuronal SH-SY5Y cells. Nutrients, 2022; 14: 3310.
19. Kim JH, Kim HY, Cho EJ. Protective effects of kaempferol, quercetin, and their glycosides on amyloid beta-induced neurotoxicity in C6 glial cells. Nat Prod Res., 2013.
20. Sharma G, Jangra A, Sihag S, et al. Bryophyllum pinnatum (Lam.) Oken: unravelling therapeutic potential and navigating toxicity. Physiol Mol Biol Plants, 2024; 30(9): 1413–1427.
21. Mady MS, Ibrahim RR, El-Sayed EK, et al. Exploring the comprehensive neuroprotective and anticancer potential of afzelin. Pharmaceuticals, 2024; 17(6): 701.
22. Kitagishi Y, et al. Dietary regulation of PI3K/AKT/GSK-3β pathway in Alzheimer's disease. Alzheimers Res Ther., 2014; 6: 35.
23. Milad R, El-Ahmady S, Singab AN. Bufadienolides of Kalanchoe species: an overview of chemical structure, biological activity and prospects for

pharmacological use. Phytochem Rev., 2014; PMC5696496.
24. Muzitano MF, et al. Quercetin glycosides from Kalanchoe pinnata: isolation, identification and anti-inflammatory activity. Phytother Res., 2006; 20(12): 1060–1064.