International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 15 Issue 06 , June - 2026

Coumarins and Neurodegeneration: Unlocking Therapeutic Pathways - A Review

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***ABSTRACT*-Alzheimer's disease (AD) is a progressive neurodegenerative disorder identified by cognitive decline, cholinergic dysfunction, and the accumulation of amyloid-β plaques. Acetylcholinesterase inhibitors (AChEIs) and NMDA (N-Methyl-D-aspartate) receptor antagonists, offer only symptomatic relief without altering disease progression. Coumarins, a diverse class of plant-derived benzopyrone metabolites, have recently gained attention for their potential neuroprotective properties. This review aims to summarize current evidence on the therapeutic prospects of coumarin derivatives in AD, with based on their acetylcholinesterase (AChE) inhibitory activity, antioxidant potential, and ability to modulate amyloidogenic pathways. Preclinical studies indicate that several coumarins can inhibit AChE, enhance cholinergic neurotransmission. However, the change of these findings into clinical applications remains limited due to challenges such as poor bioavailability, structural instability, and insufficient in vivo validation. Overall, this review highlights coumarins as promising lead molecules for AD drug development and discusses future directions, including structural optimization, toxicological evaluation, and well-designed clinical studies.**

***Keywords*-Alzheimer"s disease, Coumarin, Acetylcholine, Acetylcholinesterase inhibitors**

I.INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, representing a major global health challenge affecting millions of elderly individuals. It is a progressive neurodegenerative disorder characterized by impairments in memory, learning, and executive functions, eventually leading to severe cognitive and functional decline, associated with neuronal loss and synaptic dysfunction, which arise from multiple pathological processes rather than a single causative factor. Traditionally, AD pathology is defined by extracellular amyloid-β (Aβ) plaques (Fig 1) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein (Fig 2). These pathological changes disrupt neuronal signaling, alter

glial cell function, and trigger chronic neuroinflammation, ultimately contributing to irreversible degeneration of brain regions critical for memory and cognition, particularly the hippocampus and cortical areas.

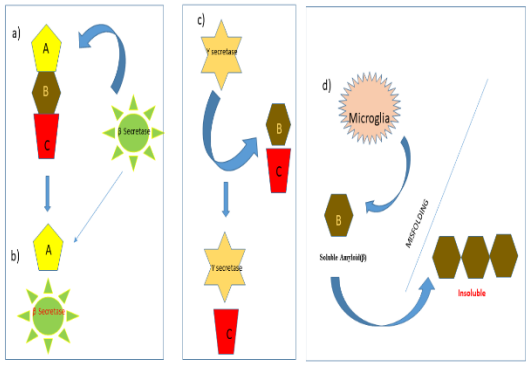

Fig 1 Formation of insoluble amyloid beta peptides a) APP Amyloid precursor protein b) Soluble APP Cleaved from the whole portion of APP c) Soluble Amyloid (β) and AICD cleaved from APP d) Microglia engulfes soluble amyloid (β), remaining soluble β amyloid clearance by microglia, misfolded soluble β converted into insoluble β deposits

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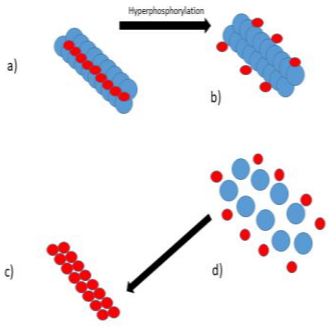

Fig 2 Transformation of soluble Tau to insoluble Tau Tangles a) Axonal microtubule associated with tau protein (Tubulin associated unit b) Tau protein dissociates after Hyperphosphorylation c) Soluble Tau protein aggregates as insoluble Tau tangles d) Axonal microtubule diassociation without tau

I. AD PATHOPHYSIOLOGY

Neurotransmission is the main process for communication with the body cells. It is done with the help of certain enzymes and neurotransmitters. Acetylcholine, a crucial chemical transmitter secreted by cholinergic neurons (Chen *et al*., 2022) for memory and thought, is reduced in Alzheimer's due to nerve cell death. Acetylcholine is typically broken down by the enzyme acetylcholinesterase to terminate a signal by preventing this breakdown, AChE inhibitors increase the amount of acetylcholine accessible in the brain. Memory, language, and other cognitive abilities could be enhanced as a result of this increased acetylcholine availability (Picciotto *et al.,* 2012) which also enhances cholinergic neurotransmission (Arora *et al*., 2025).

AD etiology remains complex and multifactorial amyloidogenic processing of amyloid precursor protein (APP) by β- and γ-secretases leads to the accumulation of toxic Aβ (Amyloid beta) fragments, especially $A\beta_{1-42}$, which aggregate into oligomers and fibrils, these aggregates initiate a cascade of events including oxidative stress, mitochondrial dysfunction, microglial activation, and synaptic toxicity (Iliyasu *et al.,* 2023). In parallel, tau protein undergoes abnormal hyperphosphorylation, causing it to dissociate from microtubules and aggregate into paired helical filaments. The resulting neurofibrillary tangles further compromise axonal transport and neuronal integrity. Genetic factors such as mutations in APP, presenilin genes, and polymorphisms in MAPT also contribute to disease susceptibility and progression (Devkota *et al*., 2025).

II. CURRENT THERAPEUTIC STRATEGIES AND LIMITATIONS

Many Indian plant-derived compounds, especially secondary metabolites, demonstrate significant acetylcholinesterase inhibitor (AChEI) activity, offering therapeutic potential against neurodegeneration. (Prajapati *et al*., 2025). The primary source of the cognitive impairments is acknowledged by the synaptic disruption, which is a significant clinical feature of AD (Wu *et al*., 2021). Coumarins a diverse group of plant-derived benzopyrone secondary metabolites have shown notable neuroprotective properties by exhibiting antioxidant, anti-inflammatory (Saadati *et al*., 2024), anti-amyloid and enzyme-inhibitory activities (Annunziata *et al*., 2020), several studies have demonstrated that specific coumarin derivatives can inhibit acetylcholinesterase (AChE) with significant potency (Sharifi *et al*., 2021), modulate glial activation, suppress oxidative stress, and effectively penetrate the blood–brain barrier (Kowalczyk *et al.,* 2025), while their structural flexibility, allowing diverse substitutions on the benzopyrone ring, makes them attractive scaffolds for developing novel anti-Alzheimer drug. However, the therapeutic potential of coumarins in AD remains incompletely understood, with challenges such as limited bioavailability, metabolic instability, potential toxicity and insufficient in vivo validation still hindering their advancement toward clinical application. Therefore, this review aims to compile and critically evaluate current research on plant-derived coumarins relevant to AD, focusing particularly on their role as acetylcholinesterase inhibitors and neuroprotective agents, also examining their mechanisms of action and highlighting the challenges and future directions needed to establish coumarins as promising lead molecules for AD drug development.

Coumarins represent a major class of natural antioxidant compounds with low molecular weight and diverse pharmacological properties. They are benzopyrone derivatives found in numerous plant species (Table 2) and are currently gaining attention for their neuroprotective effects, especially AChE inhibition. AChEI are the compounds which prevents the hydrolysis of acetylcholine into choline and acetate and which leads to normal cholinergic neurotransmission especially in AD (Rullo *et al*., 2025). As AChEI are involved in the system by inhibiting the activity of AchE, the low production of acetylcholine in the AD patient will perform its normal neurotransmission. These kinds of AChEI are already in use namely galantamine, donepezil, rivastigmine but they do not

provide complete cure for the disease, aducanumab a drug has a confined license in June 2021, clinical investigation shows that it minimizes the load of Aβ plaque but there is no relationship between improvement in patient cognitive performance (Rai *et al*., 2024), So there has been a rising focus on dementia prevention approaches. AD and dementia are heterogeneous and their different conditions arisen were by a combination of genetic, metabolic and lifestyle changes (Rosenberg *et al*., 2020). BBB (Brain Blood Barrier) is highly specific endothelial cell membrane that lines cerebral micro

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vessels (Liu *et al*., 2025), which tends to the interface between neural cells and the immune cells (Elena Zenaro *et al.*, 2017). Any therapeutics designed for targeting brain must be stable at physiological conditions and should have the efficiency to cross BBB. (Prasenjit Mondal *et al.*, 2018, Wong *et al*., 2019).

III. ACETYLCHOLINESTERASE (AChE) INHIBITION

AChE is a hydrolytic enzyme belongs to α/β hydrolase protein superfamily which stops synaptic transmission by hydrolyzing the neurotransmitter ACh. Cholinergic dysfunction triggered by the upregulation of AChE causes disrupted level of ACh leads to the depletion of ACh, which is one of the main factor for AD (Ferreira-vieira *et al.*, 2016). APP is an another responsible for the formation of plaques and tangles accumulation in brain. APP is hydrolyzed by *β*-amyloid-secreting enzyme and *γ*-secretase instead of *α*-secretase and *γ*-secretase, it releases A*β* peptides, which continues the formation of plaques and tangles (De-Paula *et al*., 2012). Up regulation of beta-secretase activity in the amyloidogenic pathway triggers Aβ peptide accumulation, which aggregates into formation of plaques (Gotz *et al*., 2004).

IV.COUMARIN CHEMISTRY

Coumarins are derived from cinnamic acid through ortho-hydroxylation, side-chain double-bond isomerization, and lactonization. The trans-form is stable and does not cyclize. The cis-form is unstable and converts back to the trans-form. Umbelliferone (7-hydroxycoumarin) (Fig 3) is considered the parent molecule of the coumarin family both structurally and biogenetically.

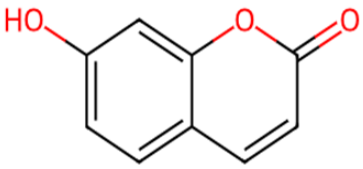


Fig.3 Umbelliferone

Plant-derived coumarins occur as Simple coumarins (hydroxylated, alkoxylated, alkylated derivatives), Furanocoumarins (with a fused five-membered ring), Pyranocoumarins (containing a fused six-membered ring) (Table 1).

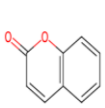
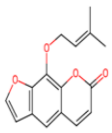
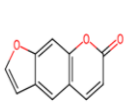
SIMPLE COUMARINS	FURANO COUMARINS	PYRANO COUMARINS
Coumarin 	Imperatorin 	Psoralen 

Table 1 : Derivatives of Coumarin

S.No	Name of the Plant	Coumarin derivatives
1.	*Apiumgraveolens* (Celery)	Apigravin, apiumetin, apiumoside, bergapten, celerin, celereoside, isoimperatorin, isopimpinellin, osthenol, rutaretin, seselin, umbelliferone, 8-hidroxy-5-methoxypsoralen.
2.	*Coriandrumsativum* (Coriander)	Umbelliferone,
3.	*Cuminumcyminum* (Cumin)	Escopoletina, bergapten
4.	*Ferula assafoetida* (Asafoetida)	Umbelliferone, coumarin-sesquiterpene complexes
5.	*Petroselinumcrispum* (Parsley)	Bergapten and oxypeucedanin 8-hydroxy-5-metoxypsoralen, imperatorin, isoimperatorin, isopimpinellin, psoralen, xanthotoxin
6.	*Pimpinellaanisum* (Aniseed)	Scopoletin, umbelliferone, umbelliprenine, bergapten
7.	*Aeglemarmelos* (Bael fruit)	Sesquiterpeniccoumarin ethers, diterpeniccoumarin ethers, triterpeniccoumarin ethers, sesterterpeniccoumarin ethers, auraptene, epoxyauraptene, marmin.
8.	*Citrus limonum* (Lemon tree)	Escopoletin, umbelliferone, bergamotin, bergapten, bergaptol, citropten
9.	*Citrus sinensis* (Orange tree)	Herniarin, scopoletin
10.	*Chamaemelumnobile* (Roman Chamomile)	Scopoletin-7-glucoside

Table: 2 Plants with the presence of coumarin derivatives

Coumarins are particularly abundant in the Apiaceae and Rutaceae families. Certain coumarins are clinically important—for example, warfarin, an FDA-approved drug, prevents intracerebral hemorrhage by inhibiting vitamin K reductase (Garg *et al*., 2020). Substitutions on the coumarin ring significantly influence biological activity. The 3rd and 4th positions are critical for interactions with the catalytic site of AChE.Substituents at the 6th and 7th positions can greatly affect potency due to steric and electronic effects. Electron-donating groups such as $–OCH_3$, –OH, and $–NH_2$ increase lipophilicity (Zeng *et al.*, 2022) and usually enhance AChE inhibition.6,7-Dimethoxycoumarin (scoparone) derivatives often show stronger AChE inhibition than other coumarins (Flores *et al.*, 2023). Unfavorable substituents at the 6th or 7th positions (Fig 4) can reduce activity due to altered molecular polarity and weaker AChE binding (Preet Anand *et al*., 2012).

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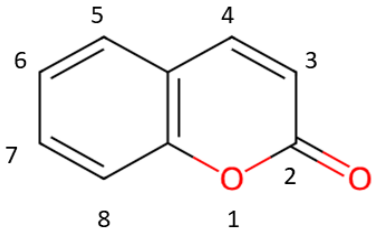

Fig 4 Structural formula of Coumarin

Many studies report that the oxa-heterocyclic ring of coumarins enables binding to a wide variety of proteins, supporting their role as neuroprotective agents across multiple neurodegenerative disorders (Mishra *et al*., 2024).

IV. MECHANISMS OF NEUROPROTECTION

Coumarins protect neuronal cells through multiple complementary mechanisms as they inhibit acetylcholinesterase, which increases cholinergic neurotransmission, coumarins have a variety of neuroprotective effects that make them for Alzheimer's disease drug discovery (Kamel *et al.*, 2023). This property has been reported for both natural and synthetic coumarin scaffolds. Additionally, they have strong anti-inflammatory activity by suppressing pro-inflammatory signalling in microglia and peripheral immune cells, and they function as antioxidants that scavenge reactive oxygen species and mitigate oxidative damage (Citarella *et al.*, 2024). Crucially, a number of coumarin derivatives have been demonstrated to decrease Aβ burden in biochemical and cell models by interfering with amyloid-β aggregation and oligomerisation, while other coumarin-based compounds decrease tau hyperphosphorylation and fibrillization collectively addressing two key pathological axes of AD. (Saha *et al.*, 2024).

V. CURRENT THERAPEUTIC STRATEGIES AND LIMITATION ANTIOXIDANT PATHWAYS

Synthetic AChEI is currently in use to treat mild to severe cognitive disorder. Antioxidants like as selenium, coenzyme Q and vitamins A, C and E have been studied for their ability to lower the risk of AD (Gualtieri *et al*., 2025). Selegiline, an antioxidant-rich monoamine oxidase B inhibitor used to treat Parkinson's disease patients, may also be helpful in treating AD, according to a modest number of clinical trials (Farlow *et al.*, 2008). World health organization (WHO) states accessible resources for neurological diseases are inadequate in most countries of the world compared with universal necessity for neurological repair (Singh *et al*., 2024), hence it need new form design and the same WHO reports around 21,000 medicinal plants are in use for various medical ailments.

VI. SYNTHETIC COUMARIN DERIVATIVES

A series of coumarin carboxamide derivatives has also been precisely designed and synthesized as possible AChE inhibitors against Alzheimer's disease (Rai *et al*., 2024) hence the naturally occurring antioxidants like coumarins have been receiving greater attention (Pedersen *et al*., 2007).

The coumarin compounds like 7-benzyloxy-4-{[(4-phenylthiazol-2(3*H*)-ylidene) hydrazono]methyl}- 2*H*-chromen-2-one,7-benzyloxy-4-({[4-(4 methoxyphenyl) thiazol 2(3*H*) ylidene] hydrazono} methyl)-2*H*-chromen-2-one, 5-amino-1-[2-(7-benzyloxy-2-oxo-2*H*-chromen-4-yl)acetyl]-1*H*-pyrazole-4-carbonitrile, 2-(7-benzyloxy-2-oxo-2*H*-chromen-4-yl)-*N*-(2-methylimino-4-phenylthiazol-3(2*H*)-yl) acetamide and 2-(7-benzyloxy-2-oxo-2*H*-chromen-4-yl)-*N*-[4-(4-methoxyphenyl)-2-methyliminothiazol-3(2*H*)-yl] acetamide have promising AChE inhibitory activity even better than donepezil which is a common drug used for AD. In an another research, evidence showed that Chromenyl Coumarate (CC) was found to be better inhibitor with the IC_{50} = 48.49 ± 5.6 nM than the reference drug donepezil with the IC_{50} = 74.13 ± 8.3 nM (Boruah *et al.*, 2018)

VII. ANTI-AMYLOIDOGENIC EFFECTS

The coumarin derivatives can produce a wide range of noncovalent compounds with diverse modes of action when combining with other compounds. Additionally, coumarin hybrids have the ability to overcome medication resistance and produce a variety of immune responses. (Xu Z *et al*., 2021). Combining two or more pharmacophores into a single molecule allows hybrid molecules to function in multiple ways and mitigate the negative effects of the individual hybrid components (Battini *et al*., 2019). The neuroprotective and cognitive-enhancing effects are because of the presence of phenolic acids which have their anti-amyloidogenic and anti-aggregant activity (Caruso *et al*., 2021). In terms of both their safety and effectiveness, it is evident that coumarin and compounds related to coumarins offer an extensive array of possible therapeutic solutions (Zhang *et al*., 2019) (Fig 5) Several spectroscopic techniques and elemental evaluation approaches have been used to produce and evaluate new coumarin derivatives as macromolecules (Ahmed *et al*., 2015). The pharmacokinetic profile of coumarin derivatives showed it had a good total polar surface area value, which revealed its noble oral ability with its high human intestinal absorption and it is not mutagenic and not an irritant. Fortunately, it revealed a safe toxicity profile (Kamel *et al*., 2023).

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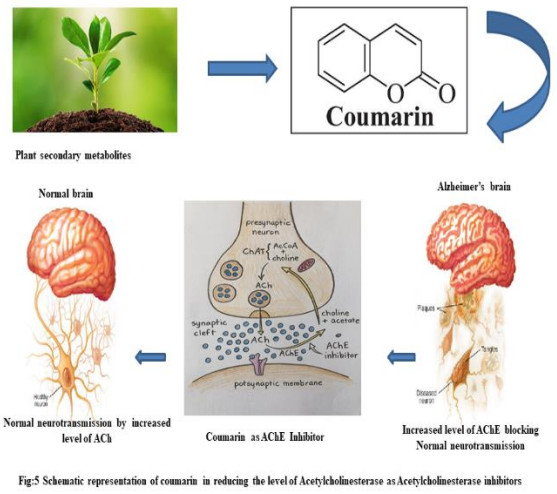

Fig:5 Schematic representation of coumarin in reducing the level of Acetylcholinesterase as Acetylcholinesterase inhibitors

VIII. BBB PERMEABILITY

The other coumarin derivatives such as esculetin, decursinol, scopoletin and mesuagenin has been already reported that the use of benzyloxy group at position 7 of coumarin scaffold has a great effect on AChE inhibitory activity (Ahammed *et al.*, 2021). Evaluation of single-target modulation to a multi-target-directed ligand formulation

develop effective drugs for the treatment of AD with new multifunctional hybrids combining coumarin in the Drug discovery of AD (Zolek *et al.*, 2024). The most promising approach for the symptomatic treatment of AD is to increase the synaptic levels of ACh in the brain by inhibiting the AChE enzyme, which is primarily accountable for its hydrolysis and termination of action (Anand *et al.*, 2014). Coumarin derivatives have reaped attention due to their pharmacological properties, encouraging investigation as potential AChE inhibitors. Additionally, the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) study profile for coumarins suggested that molecules are not toxic and have capability to cross BBB (Jaber *et al.*, 2024). This review focuses on the synthetic, semi synthetic potentials of coumarin derivatives, the natural coumarins moieties are the targets with the presence of multiple aromatic rings and electron donating groups which will increase the lipophilicity of the compound to cross the BBB of AD patients without toxicity and will show greater effects on AChE inhibitory activity.

IX. CLINICAL FINDINGS ON NATURAL AND SYNTHETIC COUMARIN DERIVATIVES

The compound 8-acetyl-7-hydroxycoumarin extracted from a plant source, *Nardostachys jatamansi* rhizomes shows a moderate inhibitory effect on AChE, with an IC_{50} value of 22.1 μM. In divergence, a semisynthetic trifluoromethyl-substituted coumarin chalcone validates a fivefold improvement in the inhibition of BACE-1 which means the β-Site APP-cleaving enzyme, achieving an IC_{50} of 3.3 μM. A semisynthetic derivative, which is a hybrid of coumarin and donepezil, displays inhibitory activity with IC_{50} values of 1.22 and 3.09 μM has been reported by Sharma *et al.*, 2022. Compound IMM-H004 (7-hydroxy-5-methoxy-4-methyl-3-[4-methylpiperazin-1-yl]-2H-chromen-2-one) is a novel coumarin derivative that showed enhanced efficacy in ameliorating global cerebral ischemia through the protection of BBB reported by Niu *et al.*, 2017.The synthesized compound [4-[3-(4-phenylpiperazin-1-yl) propoxy]-2H-chromen-2-one], a derivative of coumarin, exhibited prominent acetylcholinesterase (AChE) inhibitory activity with an IC_{50} value of 2.42 μM, which is in comparison to donepezil's IC_{50} of 1.82 Mm and its molecular docking analysis revealed that this compound interacts with all key amino acids located at the catalytic active site, mid-gorge, and peripheral anionic site of AChE, leading to enhanced inhibition of the enzyme (Singla *et al*., 2016) and the quantitative structural activity relationships of coumarin derivatives in relation to AChEI acknowledged that features such as polar surface area, octanol/water partition coefficient, and molecular flexibility show a vital role in determining BBB permeability (Liu *et al*., 2022). Coumarin is not considered a genotoxic agent, as its metabolism differs between susceptible rodent species and humans. In rats and mice, the primary metabolic pathway for coumarin involves 3,4-epoxidation pathway, leading to the production of toxic metabolites. while in humans, it primarily follows a 7-hydroxylation which is a detoxification pathway. The estimated maximum daily exposure to coumarin as dietary sources for an individual weighing 60 kg is reported as 0.02 mg/kg/day. Consequently, it is concluded that exposure to coumarin through food or cosmetic products does not create a health risk to humans (Yamada *et al*., 2022).

X. CONCLUSION

Coumarins are the compounds with several moieties exhibiting no toxic effects with oral bioavailability and have significant role in controling the AChE inhibitory activity. This review paper reveals the current research necessity for the creation of innovative therapeutic medications for an efficient treatment of Alzheimer's disease through knowledge of particular pharmacological targets. AD were a very serious neurodegenerative disease that caused memory loss and a reduction in cognitive abilities. Role of AChEI targeting Aβ peptides is an interesting approach**,** the plant derived coumarin compounds will be the potential AChE inhibitors with their possible neuroprotective properties which will be used in combinations creating hybrids and it will be the active formulated drug which can replace the synthetic drugs in the

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
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market by crossing the blood brain barrier in the human brain which ends up the formation of Aβ plaques and helps in the normal neurotransmissions.

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ISSN: 2278-0181
Vol. 15 Issue 06 , June - 2026

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