RESEARCH PAPER

Pentacyclic Triterpenoids: An Emerging Multifunctional Druggable Small Molecules to Treat Alzheimer's Disease

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Abstract:
Alzheimer's disease (AD) is the most prevalent progressive neurological illness that develops dementia; it is thought to be responsible about 60-70% of cases worldwide. Now the main trigger of death in this age range, AD is a degenerative illness that mostly affects people 60 to 65 years of age. According to epidemiological projections, the burden in underdeveloped countries may reach 107 million individuals by 2050. The clinical categorization of AD comprises four histological stages and numerous stages (I to VI) based on the progression of the disease. Pathogenesis of AD includes abnormal tau tangles in the brain, amyloid-(A) deposition plaques, and the basic amyloid cascade theory. Neuritic plaques, which resemble spheroid-shaped microscopic lesions and are surrounded by abnormal axonal terminals, are extracellular deposits of amyloid peptide (A). A comes from the amyloid precursor protein (APP).
AD-induced neuronal degeneration can be prevented by pentacyclic triterpenoids, a class of multipurpose natural compounds, and their semi-synthetic derivatives. These compounds have a variety of impacts through their interactions with several biomolecules. They are commonly consumed by all populations worldwide, indicating their safety. Systematic research on the Pentacyclic triterpenoids and their derivatives which play multiple roles in AD treatment is the main topic of the current review. Pentacyclic triterpenoids have been shown to produce cytoprotective and chemosensitizing effects as well as aid in the therapy of Alzheimer disease by engaging with the target molecule such as nuclear factor kappa B (NF-KB), cell longevity pathways, nuclear factor erythroid-derived like 2 (NrF2), free radical scavenging, and protein kinase C (PKC).

Keywords: Pentacyclic triterpenoids, Molecular targets, Biomolecule, Alzheimer's disease

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1. Introduction:

AD is a neurological disorder that is mostly predominant in elderly people, which significantly reduces patients' quality of life. It is the most common progressive neurological condition characterize by dementia, responsible for 60-70% of occurrences worldwide. The degenerative disease AD primarily affects older individuals between the ages of 60 and 65 and is currently the most common cause of death in this age group [1]. Epidemiological estimates indicate that by 2050, the burden in developing nations could increase to 107 million people. The Global Burden of Disease Study found that AD is one of the diseases with the greatest rate of increase among the top causes of death [2, 3]. According to the disease's course, the clinical classification of AD includes multiple phases (I-VI) and four histological stages. The primary amyloid cascade theory, amyloid-(A) deposition plaques, and aberrant tau tangles in the brain are all components of AD pathogenesis [4]. Amyloid peptide (A) is deposited extracellularly in spheroid-like microscopic lesions (neuritic plaques), which are encircled by aberrant axonal terminals. A is a protein of enormous size composed of the APP. Aβ is produced through the proteolytic breakdown of membrane-bound β-amyloid precursor protein. Whereas NFT and amyloid pathology are both common features of AD, there is a lack of understanding on the relationship between the two pathologies. Numerous studies imply a connection between these two clinical symptoms of AD and the attack by free radicals, or oxidative stress [5, 6].
It is commonly acknowledged that oxidative stress rises with age and can be viewed as a considerable age-depending factor increasing the susceptibility of the brain to numerous neurodegenerative illnesses include amyotrophic lateral sclerosis, AD, and Parkinson's disease. An early and noticeable characteristic of AD's susceptible neurons is increased oxidative damage. Many studies In vivo, In Vitro as well as biopsy of AD's patient's shows increases in oxidative stress induced neuronal damage in AD [7, 8].

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1.1 AD aetiology and pathogenesis:

1.1.1 Aetiology of AD:

The main causes of the development of AD and other neurodegenerative diseases are oxidative stress, aging, genetic predisposition, and brain ischemia damage associated with cardiovascular disease (Fig. 1). It is now known that a number of CNS injuries, particularly brain trauma, Increase the chance of AD. Inflammation and cytokine production rise as a result of these attacks. Cerebral ischemia damage and AD appear to be two equally distinct CNS disorders at first glance. However, decades of research have shown that they have a common path that culminates in cell death, in addition to starting with the same predispositions.

The pathophysiology of AD and brain ischemia is similar, resulting in neuronal death and the build-up of Aβ peptide. The destruction of the central nervous system, including head trauma, can cause AD. These assaults induce swelling and increased production of cytokines.[6] On the surface, AD and cerebral ischemic injury could appear to be two quite distinct CNS disorders. However, it has been demonstrated that both begin with similar predispositions and follow the same path that leads to cell death. The pathophysiology of AD and brain ischemia shares commonalities that have recently been brought to light; these similarities lead to the accumulation of Aβ peptide and the ensuing neuronal damage [9].

An increasing amount of evidence suggests that cerebral ischemia may possibly play a role in the origin of AD. The majority of AD occurrences occur in adults over 65; younger people are rarely impacted. This is a very complex and irreversible process that reduces the weight and volume of the brain. It also results in the loss of synapses and the growth of ventricles in certain parts of the brain. There are also several illnesses, such as hyperglycemia and improper cholesterol homeostasis [10] the bridging integrator 1 (BIN1) gene is identified as the key danger factor for AD, along with APOE [11, 12, 13].

The brain weighs between 1200 and 1400 g on average when it is removed during an autopsy. Brain weight begins to decrease between the ages of 45 and 50, reaching its lowest point at 86. Even people without dementia contain Aβ plaques and NFTs, two well-known pathology indicators of AD, in their aging brains [14].

The oxygen free radicals oxygen (O_2., .OH), H_2O_2, singlet, and hypochlorous acid are referred to as reactive oxygen species (ROS) [15]. The brain metabolism of iron is altered in AD patients. The brains of AD patients contain a large number of oxidative stress-derived macromolecules. Antioxidant enzymes such as glutathione reductase and superoxide dismutase are also thought to be depleted in AD pathophysiology [16]. A change in anticholinesterase (AChE) activity is associated with acetylcholine deficit in AD. In the beginning stages of AD, ROS-induced oxidative stress brought on by an imbalance in redox metal homeostasis is crucial. Oxidized DNA, hydroxyl radical adducts, lipid peroxides, advanced glycation end products, and other important markers of oxidative stress have been discovered to be present in the AD brain [17]. The multifactorial aetiology of AD, involving genetic, environmental, and lifestyle-related risk factors, is summarized in Fig. 1.

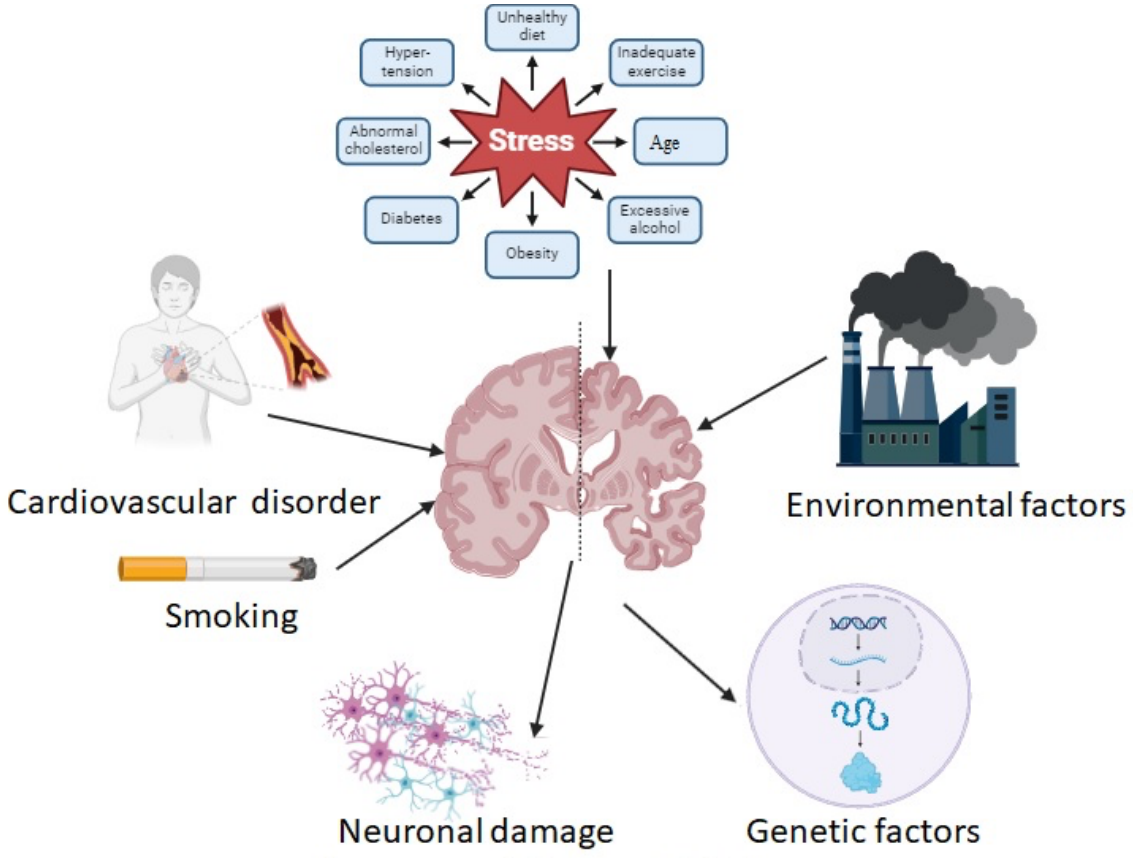


Fig. 1. Aetiology of AD.

1.1.2. Pathogenesis of AD:

Amyloid accumulation can be used to explain the pathogenesis of AD, and NFT alterations can be used to explain the pathogenesis of AD. The plaque like deposits exhibit a wide range of sizes and shapes. The majority of them do not display neuronal abnormalities or glial cell accumulations, nor do they have pathologically changed argyrophilic nerve cell processes. It appears that the nerve cells inside the deposits are virtually unchanged [18]. It is crucial to differentiate between amyloid deposits and neuritic plaques as a result. As demonstrated in Fig. 2, there is significant diversity in the accumulation of amyloid deposition in its early phases. Only three stages, such as A, B, and C, can be distinguished. In Stage A the first low density amyloid deposits appear in the isocortex, particularly in the basal areas of the frontal, temporal, and occipital lobes. The hippocampal formation is still free of amyloid plaques. Amyloid bands that are weakly pigmented and often have boundaries that are unclear are seen in the parvocellular layer of the presubiculum and in the entorhinal layers Pre-β and Pre-γ. Stage B shows amyloid deposits are found at medium levels in almost all isocortical association regions. The only areas with deposits, or very few, are the primary motor field and the primary sensory regions. The belt areas and rather broad portions of the frontal and parietal lobes next to the central region have occasional amyloid deposits. Globular amyloid deposits in glial layers I–VI vary in force [19]. In practically every isocortical region, Stage C displays densely packed deposits that virtually maintain their laminar distribution's structure. Therefore, amyloid depositions in primary isocortical areas are the main characteristic of Stage C [20].

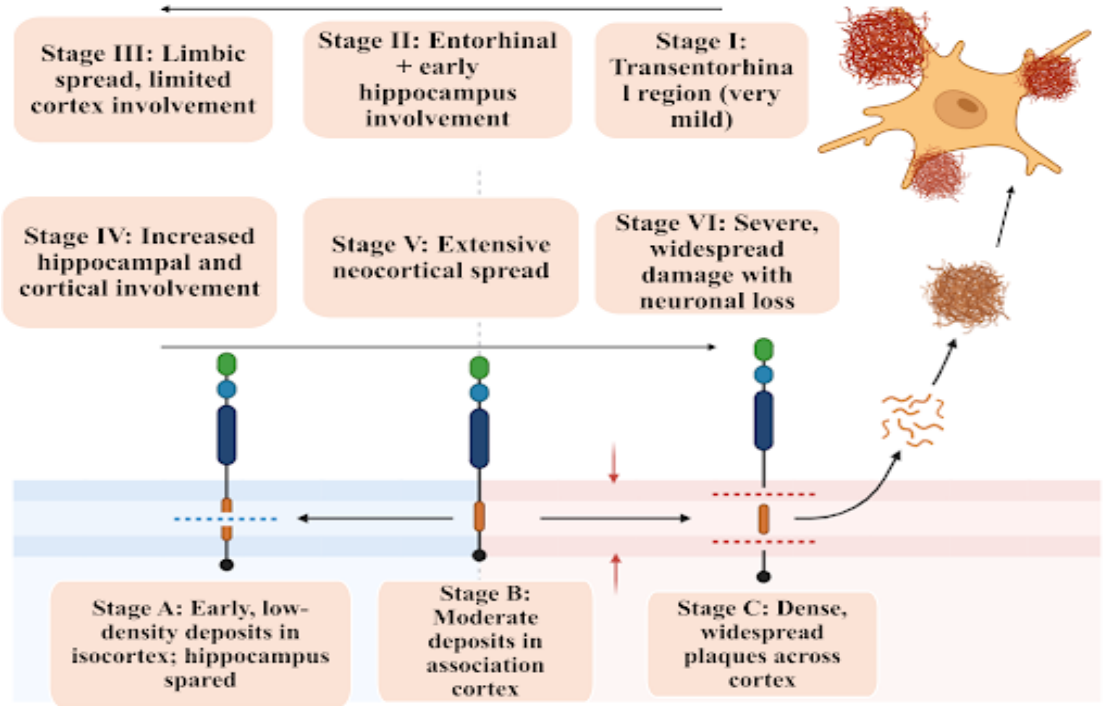


Fig. 2. Neuropathological staging of AD showing amyloid deposition (Stages A–C) and neurofibrillary tangle progression (Stages I–VI).

Stages I through VI of neurofibrillary changes-based neuropathology are depicted in Fig. 2. In stage I area responsible for the least severe damage is the Trans entorhinal region. The transition zone between the entorhinal region and the adjacent temporal isocortex is complex. This region is distinct because the Pre-α area traverses exterior cortical layers. Over time, pyramidal cells gradually emerge from star-shaped Pre-α neurones. Throughout Stage I, just a handful of these changes occur. A few solitary NFTs may also show up in the right entorhinal layer [21, 22, 23]. Stage II is an advanced stage that demonstrates how NT and NFT are involved in transentorhinal Pre-α. They lose part of their density when they approach the proper entorhinal Pre-α. NFT is found in trace amounts in the wedge-shaped extremities covering subiculum of the hippocampal region CA1. The thalamic antero-dorsal nucleus and the magnocellular forebrain nuclei either remain unchanged or experience only slight changes. One may infrequently observe isolated NFTs in isocortical association areas. Stage III shows Pre-α layer involvement in the entorhinal and transentorhinal areas is evident at this stage. Many of Pre-alpha's projection neurones have an NFT. NT, which is present in many of these cells' dendrites, usually makes it possible to comprehend the size of the dendritic tree. In NFT, "ghost tangles" were first discovered in the 19th century. There are either very slight changes or almost no changes in the isocortex. NFT and NT are dispersed in the third and fifth layers of the occipital association area, temporal, and frontal, in certain individuals. In layer-III, others only display slight, randomly scattered NP [20].

The fourth step has a particularly significant impact on the pre-alpha layer. Ghost tangles are abundant in the

entorhinal and transentorhinal areas of the brain. The layers Pri-α and Pre-β are also equally important. A minor affection is also observed at the fascia dentata, accompanied by tangles of multipolar CA4-nerve cells. There is just slight damage to the basal portions of the claustrum. Large neurones in the basal portions of the accumbens nucleus and the putamen may also show NFT. Nuclei in the tuberomammillary and reuniens areas are more severely affected [24, 25]. Stage V shows huge changes with a lot of ghost tangles in layer Pre-alpha. The deep layer Pri-α is severely impacted and appears as a band because of the widespread NT. Additionally, the Pre-β and Pre-γ layers are clearly affected. The parvocellular layers of the parasubiculum and transsubiculum both have a lot of NT and very small NFT. However, the major impairment of the isocortex is the main feature of stage V. Basal portions of the medial facies and the whole inferior facies of the temporal lobes and the occipital lobes as well as the retrosplenial area are the only affected areas when the isocortex is only slightly affected. These are the antero-basal areas of the insula and orbitofrontal cortex when there is more significant compromise of the isocortex. Furthermore, some NFT and NT are visible in the hypothalamus and substantia nigra. In stage VI, each of these changes is more obvious. Numerous ghost tangles are present along with a notable loss of nerve cells in the Pre and Pri alpha layers. But sometimes, glial cells degenerate and regenerate these tangles. A dense network of NT and numerous microscopic NFT are observed in the parasubiculum and transsubiculum. It is easier to discern between stages V and VI thanks to the fascia dentata. The presence of numerous ghost tangles, a notable loss of neuronal cells, and characteristic NT stripes set CA1 apart at the top half of the stratum radiatum (SR) and stratum oriens (SO). The distinct NT stripes in the top half of SR and SO, the presence of numerous ghost tangles, and a significant loss of neuronal cells distinguish CA1 from other parts of the brain [23, 24, 25].

When an autopsy or biopsy reveals AD histopathologically, the diagnosis is made. Neuronal damage markers for AD include tau levels and MRI atrophy. A less costly but more invasive test is to look for Amyloid-β, total tau protein, and hyperphosphorylated tau peptide in the CSF [26]. Another promising blood test that shown validity and reproducibility in smaller studies was the serum microRNA profile screen [27]. However, no differences in the diagnostic effectiveness of amyloid PET imaging biomarkers, p-tau ratio, and CSF amyloid-β have been found, suggesting that the best test is reliable in terms of price, availability, and convenience. Table 1 summarizes the major biomarkers associated with AD, highlighting their sample sources, underlying mechanisms, and clinical significance in diagnosis and disease progression.

Table 1: Biomarkers of AD

Category	Biomarker	Sample Type	Mechanism / Pathological Relevance	Clinical Significance	Reference
Amyloid biomarkers	Aβ42	CSF	Decreased due to extracellular deposition as amyloid plaques derived from APP cleavage	Early diagnostic marker of amyloid pathology	[4]
	Aβ42/Aβ40 ratio	CSF / Plasma	Reflects amyloid burden more accurately than Aβ42 alone	Improves sensitivity and specificity in diagnosis	[26]
Tau biomarkers	Total tau (t-tau)	CSF	Marker of neuronal damage and degeneration	Elevated in AD; correlates with disease severity	[26]
	Phosphorylated tau (p-tau)	CSF / Plasma	Reflects tau hyperphosphorylation and neurofibrillary tangle formation	Specific biomarker for AD pathology	[26]
Neurodegeneration markers	MRI (brain atrophy)	Imaging	Structural degeneration, especially hippocampal atrophy	Diagnostic and disease progression marker	[26]
Oxidative stress markers	Lipid peroxides (e.g., 4-HNE)	Brain / Blood	Product of lipid peroxidation induced by ROS and Aβ	Indicates oxidative damage in AD brain	[17,29]
	Oxidized DNA	Brain	DNA damage due to ROS	Marker of genomic instability	[17]

	Protein oxidation products	Brain	Oxidative modification of proteins	Reflects cellular damage	[17]
Inflammatory biomarkers	TNF-α	Plasma / Brain	Pro-inflammatory cytokine induced by oxidative stress	Contributes to neurotoxicity and progression	[28]
	IL-1β	Plasma / Brain	Mediates inflammatory cascade	Associated with neuronal injury	[28]
	IL-6	Plasma / Brain	Chronic inflammation mediator	Correlates with disease progression	[28]
Metabolic biomarkers	NAD+ depletion	Brain	Reduced due to PARP activation following DNA damage	Leads to impaired ATP production and mitochondrial dysfunction	[28]
Mitochondrial biomarkers	Mitochondrial dysfunction	Brain	Increased ROS, reduced mitophagy, membrane potential changes	Central to AD pathogenesis	[30]
Genetic biomarkers	APOE	Blood (DNA)	Major genetic susceptibility factor	Increases risk of AD	[11]
	BIN1 gene	Blood (DNA)	Identified as key risk factor	Associated with disease development	[12,13]
Biochemical diagnostic markers	CSF Aβ, total tau, p-tau	CSF	Core biomarkers for AD diagnosis	Reliable but invasive diagnostic tools	[26]
Emerging biomarkers	Serum microRNA	Blood	Reflects gene regulation changes in AD	Promising non-invasive diagnostic marker	[27]

1.2 Oxidative stress and AD:

Oxygen and nitrogen-based compounds that contain unpaired electrons produce reactive oxygen species (ROS). The main process that produces free radicals is oxidative stress and is highly reactive towards the electron from other molecule. The hazardous free radicals created by the body interact with lipids, proteins, and nucleic acids to cause cellular damage if they are not eliminated or neutralised [6]. A significant and early characteristic of susceptible neurons in AD is increased oxidative damage. It was documented a robust inverse connection between neuronal oxidative damage and neuronal size among cases of AD [7]. According to new research, one of the main causes of cognitive aging and neurodegenerative illnesses like AD may be cumulative oxidative stress. A comparative overview of natural compounds and synthetic drugs used in the management of AD is presented in Table 2.

Table 2: Comparison of Natural Compounds vs Synthetic Drugs in AD

Parameter	**Natural Compounds (e.g., Pentacyclic Triterpenoids)**	**Synthetic Drugs (e.g., Donepezil, Memantine)**	**Reference**
Source	Derived from plants (leaves, bark, fruits, oils)	Chemically synthesized molecules	[32,47]
Mechanism of action	Multi-target: antioxidant (Nrf2 activation), anti-inflammatory (NF-κB inhibition), anti-amyloid, anti-tau	Primarily single-target: AChE inhibition (Donepezil), NMDA receptor antagonism (Memantine)	[38,26]
Oxidative stress modulation	Strong antioxidant activity; scavenges ROS and enhances endogenous antioxidant enzymes	Limited direct antioxidant effect	[28]
Anti-inflammatory effects	Inhibits cytokines (TNF-α, IL-1β, IL-6), reduces microglial activation	Moderate anti-inflammatory effects	[55]
Effect on amyloid pathology	Reduces Aβ aggregation and plaque formation	Does not directly reduce amyloid burden (symptomatic relief only)	[69]
Effect on tau pathology	Inhibits tau hyperphosphorylation and aggregation	Minimal or indirect effect	[89]
Neuroprotection	Promotes neuronal survival, synaptic plasticity, and mitochondrial function	Provides symptomatic cognitive improvement	[44]

Side effects	Generally low toxicity; widely consumed and considered safe	Common side effects: nausea, dizziness, headache, gastrointestinal disturbances	[32]
Blood–brain barrier (BBB) permeability	Some compounds show good BBB penetration (e.g., triterpenoids)	Designed for BBB permeability	[62]
Clinical use	Mostly preclinical and experimental; limited clinical trials	Approved and widely used in clinical practice	[26]
Therapeutic approach	Disease-modifying potential (multi-target action)	Symptomatic treatment (does not halt disease progression)	[103]

Here, we compile the most recent research on how neuronal oxidative stress affects DNA damage, mitochondrial malfunction, and epigenetic modifications linked to AD and cognitive aging. Pro-inflammatory gene transcription, neurotoxicity, redox imbalance, genomic instability, and the production of cytokines including TNF alpha, IL-1, and IL-6 can all be caused by mitochondrial ROS. NAD+, a cofactor for numerous metabolic processes and a donor in the synthesis of ATP, is depleted by kinases and PARP, which are activated by DNA damage, according to the idea. The necessity for ATP synthesis and oxygen consumption rises when NAD+ levels fall, leading to mitochondria coupling in an effort to satisfy high energy demands. Further DNA damage is caused by mitochondrial coupling, which also raises free radicals, lowers mitophagy, and increases membrane potential [28]. The pathophysiology of tardy-onset, sporadic AD exhibits According to the theory of the mitochondrial cascade, age-related declines in mitochondrial activity impact APP processing and expression, resulting in amyloid beta oligomers that build up into plaques in AD. Lipid peroxidation is caused by amyloid beta, which is an efficient source of oxidative stress, as indicated by protein-bound 4-hydroxy-2-trans-nonenal. Amyloid beta's hydrophobic properties enable it to live in the lipid bilayer, and cell death results from the covalent attachment of -hydroxy-2-trans-nonenal to neuronal proteins [29]. In AD, tau hyperphosphorylation and neurofibrillary lesions are caused by suppression of phosphatase 2A and glycogen synthase kinase (GSK) 3β activation, which is brought on by ROS and mitochondrial breakdown [30]. Additionally, HNE alters the nicastrin receptor for γ-secretase substrates, which improves the binding of APP and probably raises the production of Aβ [31]. Fig. 3. illustrates the role of oxidative stress in neuronal damage, highlighting β-amyloid deposition, tau pathology, mitochondrial dysfunction, and subsequent cognitive decline.

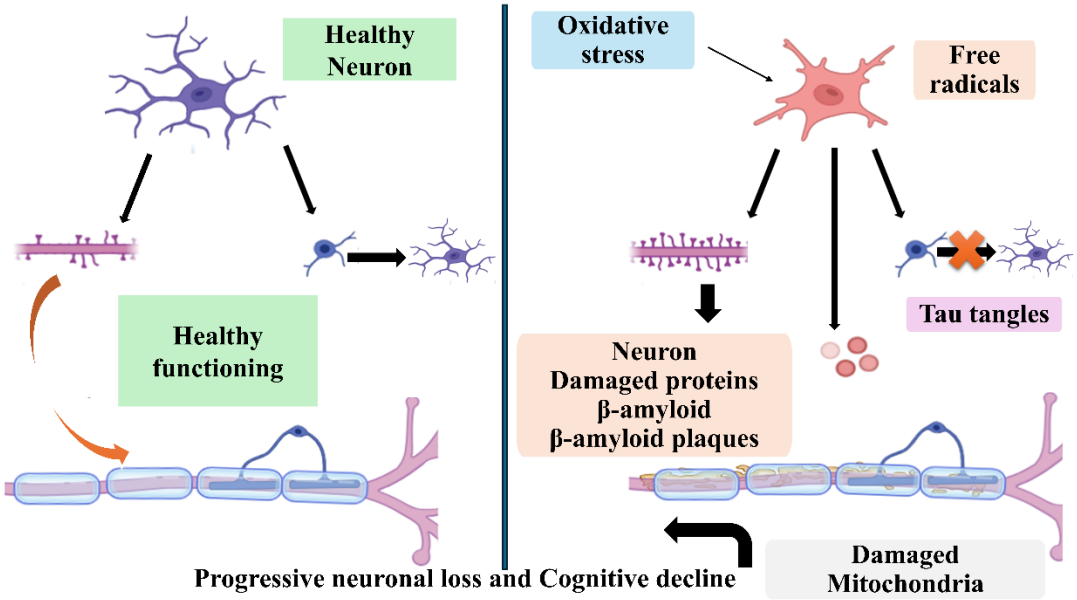


Fig. 3. Role of oxidative stress in AD progression.

2. Pentacyclic triterpenoids:

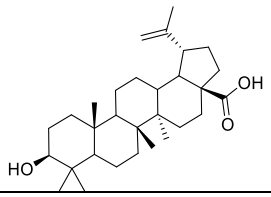
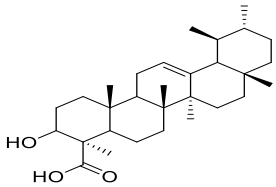
Pentacyclic triterpenoids are found in many plants and have been shown to interact with a variety of biomolecules to produce a wide range of effects. Their widespread usage and ease of access by people worldwide indicate their safety [32]. The semisynthetic and/or synthetic derivatives of pentacyclic triterpenoids can therefore be envisioned as a treatment for AD. Ursanes and lanostanes have six members, while lupanes and hopanes have five members. Pentacyclic triterpenes have a 30-carbon backbone. Secondary metabolites called pentacyclic triterpenoids are found in fruit peels, leaves, and stem bark, particularly in Mediterranean plant species. Their availability ranges from 0.1 to 3% [33, 34]. Numerous semisynthetic and synthetic derivatives of naturally occurring pentacyclic

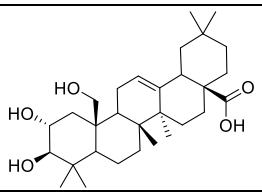
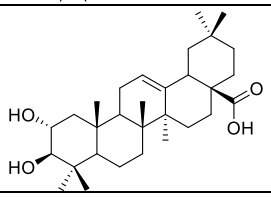
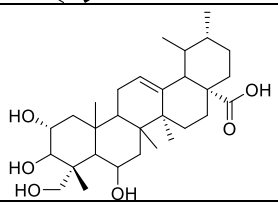
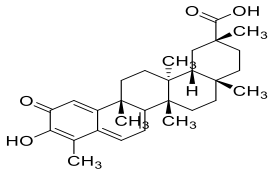
triterpenoids (PTs) have been shown to stimulate Nrf2 signaling [35, 36]. Nrf2 inducing action has been reported for the most powerful synthetic Pentacyclic triterpenoids, such as imidazole and methyl ester derivatives of CDDO (2-cyano-3,12-dioxooleana-1,9 (11)-dien-28-oic acid). These CDDO compounds are thought to be promising drugs, and some of them have already started clinical studies. The interaction between naturally occurring Pentacyclic triterpenoids and Keap1's 16-mer peptide binding domain was assessed. The cytoplasm contains a combination with Nrf2, which is inhibited by Keap1. The Nrf2 in the cell nucleus is stabilized by electrophiles during oxidative stress. Phase II antioxidant enzyme induction results from nuclear translocation of Nrf2 and subsequent transcription of the associated mRNAs [37]. A key regulator of the antioxidant system, Nrf2 is in charge of constitutive production of antioxidant proteins and phase II detoxifying enzymes. This route is complicated, as evidenced by the vast number of biomolecules involved in Nrf2 regulation. NF-κB-p65, GSK-3β, Nrf2, p62, and p38 levels are altered in AD. A substantial amount of research has examined Nrf2's capacity to lower oxidative stress, inflammation, and mitochondrial dysfunction in a range of AD models [38]. Nrf2 inducers are advantageous as strong anti-AD medications. The search for NRF2 activators to treat or prevent AD has been intense. Several Nrf2 stimulants have developed into clinical trials for the treatment of AD after being confirmed in preclinical models[39, 40, 41]. The most effective biomolecule for nrf2 translocation to neuroprotection is pentacyclic triterpenoids [42, 43, 44, 45, 46].

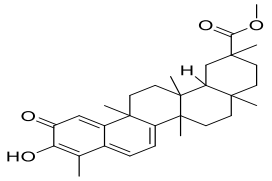
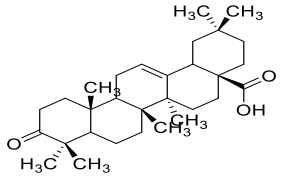
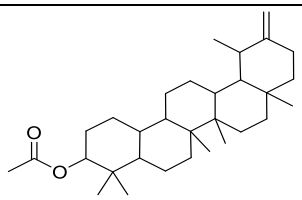
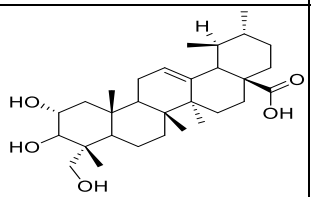
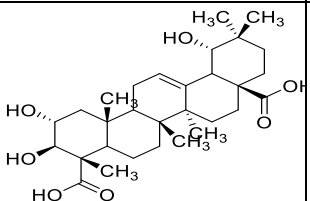
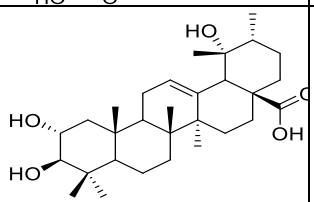
3. Pentacyclic triterpenoids as a therapeutic agents to treat AD:

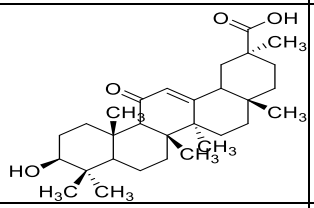
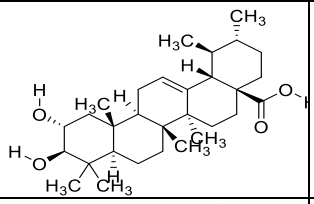
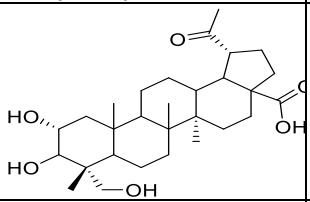
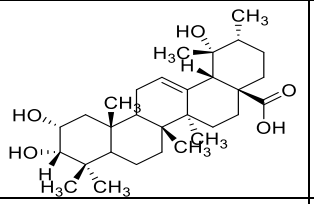
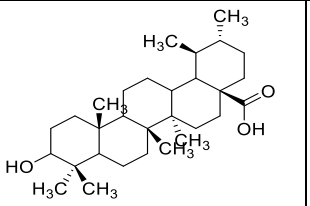
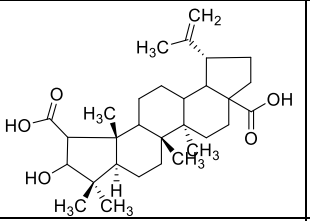
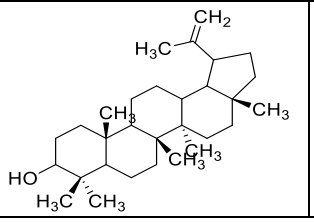
Elevated stress levels and global population aging are the main factors contributing to the rise in neurological illnesses. Individuals' life and health are severely impacted by AD, which has grown to be a major social problem [47]. Despite the approval of certain pharmaceutical treatments for the treatment of neurological illnesses, these methods are still mainly ineffective. In order to mitigate the effects of neurodegenerative diseases, including AD (AD) and other neurodegenerative disorders, it is imperative to investigate new nature-based nutraceuticals. Certain triterpenoids and their derivatives have neuroprotective and cognitive-improving properties that make them promising treatments for neurological conditions [44]. Their primary defense tactic is chemical defense, which involves creating a vast variety of bioactive secondary metabolites, including terpenes and their derivatives. Because of their wide range of bioactivities, including anti-inflammatory, antioxidant, and anti-cancer effects, this largest and most varied category of plant secondary metabolites also treats a number of illnesses. It is therefore crucial to assess terpenes' neuroprotective potential as depected in Fig. 3. [42]. Triterpenoids' chemical structures do contribute to their capacity to suppress cholinesterase activity. Future studies on medication discovery and development for the treatment of AD are encouraged because terpenoids contain anti-cholinesterase qualities [48]. A varied class of naturally occurring substances that are widely distributed in plants, triterpenoids have a number of potential neuroprotective [49] actions, including anti-inflammatory, antioxidant, Nrf2, Nfkb, and many more as depicted in Table 3. Few pentacyclic triterpenoids were mentioned below for the neuroprotection.

Table 3. Biological sources, structures, plant parts, and molecular targets of pentacyclic triterpenoids for Alzheimer's treatment

S. no.	Name of tritepenoid	Structure of triterpenoid	Source and part use for extraction	Molecular targets	Reference
1	Betulinic acid		*Vitex negundo* L.; Leaves	cAMP/cGMP and BDNF, TNF-α, IL-1β, and IL-6	[51,53]
2	Boswellic acid		*Boswellia serrata*; Gum resins	5-LOX/COX, amyloid plaques, and neurofibrillary tangles, Nrf2 and HO-1,inhibitor of nuclear factor-kappa B alpha (IκBα) and p65. TNF-α and interleukin-1 beta (IL-1β), 5-lipoxygenase.	[55,47,59]

				Cathepsin G, and microsomal prostaglandin-E synthase (mPGES)-1, pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, and IL-6	
3	Arjunolic acid		*Terminalia arjuna*; Bark		[61]
4	Maslinic acid		Orujo olive oil; Oil	Nuclear factor-kappa B	[65]
5	Madecassic acid		*Centella asiatica* (L.); Essential oil of *Centella asiatica* (L.)		[66]
6	Celastrol		*Celastrus orbiculatus*; Root of god thunder vine	Enhances transcription factor EB (TFEB)-mediated autophagy and mitigates Tau To directly inhibit the ROS producer NADPH oxidase COX enzymes Inhibition of IKKb by celastrol prevented NFκB activation and inhibited BACE-1 expression Increase the HSF1 ChIP signal in hippocampus Promotes the degradation of phosphorylated MAPT/tau aggregates both in cells and in the brain of P301S MAPT/tau and 3XTg	[72,74,69,114]

7	Pristimerin		*Celastrus hypoleucus*; Roots		[75]
8	Oleanolic acid		*Orujo olive oil*; Olive oil	Inhibited the transcription and secretion of inflammatory cytokines IL-6, TNF-α, and IL-1β in amyloid-beta peptide (Aβ)-activated astrocytes Inhibited βamyloid aggregation and fibril formation.	[75]
9	Tarexerol acetate		*Codieaum variegatum*; Bark		[86]
10	Asiatic acid		*Centella asiatica* (L) Urb; Whole plant	via AKT/GSK-3β signaling pathway in SH-SY 5Y neuroblastoma cells tau hyperphosphorylation via regulating PI3K/Akt/GSK-3β signalling apoptosis in SH-SY5Y cells	[118,89]
11	Bartogenic acid		*Barringtonia racemosa* Roxb; **Fruits**		[32]
12	Tormentic acid		*Perilla frutescens* (L.) Britt; **Leaves**	Suppressed pro-inflammatory markers and NF-κB p65 nuclear translocation in BV2 cells after Aβ exposure.	[89]

13	Glycyrrhetic acid		*Glycyrrhiza glabra*; **Roots**	Inhibited GSK3β	[101]
14	Corosolic acid		*Lagerstroemia speciosa*; **Leaves**	Bind to tau protein to inhibit the fibrillar network, preventing AD.	[104]
15	23-Hydroxy butulinic acid		*Pulsatilla chinensis*; **Roots**		[105]
16	Euscaphic acid		*Geum japonicum* Thunb; **Whole plant**	AChE inhibitory activity	[108]
17	Ursolic acid		*Salvia officinalis and Ocimum sanctum Linn*; **Leaves**	Via inactivation of NF, STAT3/6, Akt/mTOR pathways via the PI3K-AKT, MAPK Akt/mTOR pathway	[112]
18	Ceanothic acid		*Zizyphus jujuba* Mill. var. *spinosa* (Bunge); **Roots**	alleviate Tau hyperphosphorylation	[113]
19	Lupenol		*Cichorium spinosum*; **Aerial parts**	inhibits BACE1 Microtubule-associated protein tau	[117]

Betulinic acid:

In a dose-dependent way, Betulinic acid (BA) showed neuroprotective effects. In addition to demonstrating notable increases in cAMP, cGMP, and BDNF levels, BA was also able to restore behavioural parameters, re-establish cerebral blood flow, and control inflammatory and oxidative stress markers. Subjected to histopathological analysis, the groups treated with betulinic acid exhibited less microgliosis and fewer pathological anomalies like those of ill rats' brains. The putative neuroprotective effects of betulinic acid in restoring hippocampus neurochemistry and cognitive impairment in vasodepressors may account for the observed result [50]. Neurobehavioral tests (passive avoidance and spatial memory test, anxiety, locomotion, depression, and motor coordination) were used to

examine the psychological impairments associated with AD in the experimental groups. The proportion of fEPSP slope, PS amplitude, and PS AUC following HFS in AD rats can be increased by betulinic acid, according to the hippocampus's electrophysiological characteristics [51, 52, 53].

Boswellic acid:

The function of the Wnt/β-catenin pathway in Boswellic acid (BosA) preventive action against aluminum-induced AD is explained by Mohamed et al., 2022. The results showed that BosA significantly corrected the learning and memory deficits caused by the AlCl 3 therapy. Furthermore, treatment with BosA markedly lowered acetylcholinesterase levels and decreased expression of amyloid-beta (Aβ). Additionally, BA decreased lipid peroxidation, increased total antioxidants, and mitigated the higher brain levels of tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). In fact, when AlCl 3 was introduced, BA significantly suppressed β-catenin, pGSK-3β (Ser 9), and brain-derived neurotrophic factor. Siddiqui et al. (2021) showed that BAs influence a number of signalling pathways and molecular targets that are crucial throughout AD, including neurofibrillary tangle formation (NFTs), Nrf2, NF-kB, cholinergic, 5-lipoxygenase/cyclooxygenase, and amyloid-beta (Aβ). ARE-binding BAs may alter the 5-LOX/COX pathway in arachidonic acid metabolism, stimulate Nrf2, and inhibit NF-kB and AChE activity. Additionally, BosA stopped amyloid plaques (Aβ) and neurofibrillary tangles (NFTs) from causing AD-related neurotoxicity and inflammation [54, 55, 56, 57].

The interactions between four different BosA derivatives and the 5-lipoxygenase enzyme were investigated by Bolbolian et al. 2020 using molecular dynamics modelling. To mimic the enzyme, it was also carried out independently. The Cα-RMSD analysis reveals that BosA derivatives have a negligible effect on the enzyme's stability. The computation of the radius of gyration of the enzyme shows that ligands have no effect on the overall shape of the protein. Both in the presence and absence of BosA derivatives, the relative molecular weight (RMSF) values of the enzyme residues were measured.The results of molecular dynamics modelling consistently corroborate the experimental data about the inhibitory effect of the aforementioned drugs on 5-lipoxygenase [58]. According to Rajabian et al. (2020), the BA regulates apoptotic proteins (such as pro-apoptotic caspase-3 and anti-apoptotic bcl-2), neurotrophic factors (such as BDNF), and redox status. They have been shown to be effective in the treatment of cholinergic problems and inflammation [59].

Arjunolic acid:

Research on the neuroprotective qualities of asiatic acid (2α, 3β, 23-trihydroxyursan-12-en-28-oic acid, 3) and its derivatives has shown that free C(28)-CO 2 H and the triol groups are essential for reducing the neurotoxicity brought on by (Aβ), according to Facundo VA et al. (2005) [60]. Terminalia arjuna contains a pentacyclic triterpenoidal saponin called arjunolic acid (AA), which is widely known for its antioxidant qualities. We suggested testing its antioxidant capacity in rats that had been exposed to middle cerebral artery occlusion (MCAO) in order to prevent focal cerebral ischemia reperfusion (I/R) damage. Through the regulation of malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide (NO), protein carbonyl content, and mitochondria-generated reactive oxygen species, AA protected the neuronal damage caused by I/R. The activity of antioxidant enzymes and Na+–K+ ATPase were also regulated by it [61]. These compounds are potentially useful models for the development of novel, multifunctional drugs for the treatment of AD, according to our findings regarding the anti-inflammatory and anticholinesterase properties of arjunolic acid, the literature data on the oxidative stress reduction property of both acids, and the slight structural difference between AA and asticacids. Arjunolic acid is the main component present in "Mofumbo" root, with fatty acids and monosaccharides present in trace levels. It is therefore a serious competitor. AA, arjungenin, arjunglucoside I, sericic acid, and arjunetin are among the oleanane-type triterpenes and their glycosides from Terminalia arjuna (Combreatceae) bark that are shown to have the ability to inhibit acetylcholinesterase. The investigations' foundations include molecular-docking research, acetylcholinesterase (AChE)-inhibitory activity tests, and in silico pharmacokinetic and biomimetic experiments. The determined pharmacokinetic parameters suggest that arjunetin and arjunglucoside I can penetrate the blood–brain barrier [62].

Maslinic acid:

According to Huang et al. (2011), pro-degenerative cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are produced by reactive astrocytes and enhance inflammation and neuronal damage in the brain [63]. Cell viability was enhanced, the Bcl-2/Bax ratio was raised, and Bax expression was reduced by MA pretreatments. MA pretreatments maintained glutathione levels and reduced the production of reactive oxygen species, tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 that was subsequently produced by β-Amyloid peptide. Treatment with abeta increased the expression of nuclear factor-κ B (NF-κB), mitogen-activated protein kinase, p47phox, gp91phox, and advanced glycation end product receptor (RAGE) [64]. The biological properties of maslinic acid and its derivatives are diverse and include anti-inflammatory, anti-cancer, anti-diabetic, antibacterial, neuroprotective, and hepatoprotective effects [65].

Madecassic acid:

According to one study, in the Neuro-2a (N2a) neuroblastoma cell line, asiatic acid and madecassic acid (MadA) exhibit neurite outgrowth. MadA treatment of N2a cultures resulted in a dose-dependent increase in neurite extension and combined length of neurites per

cell, but a decrease in the proportion of neurite carrying cells. While the percentage of cells harboring neurites was not significantly changed by treating N2a with MadA, there was a dose-dependent increase in neurite extension and total length of neurites per cell. According to research, AA and MadA improve the structure of neurons in N2a cultures [66]. Scientist Roja created an in silico method to use Flare software to screen 20 pentacyclic triterpenoid plant chemicals against known VaD targets. A number of metrics, including intermolecular interaction energies, binding energies, and dock scores, were examined and contrasted across the chosen ligands. S-Adenyl homocysteine hydrolase, Acetylcholinesterase, and Butyrylcholinesterase were identified as significant VaD targets. Only three of the 20 pentacyclic triterpenoids that were examined—betulinic acid, ambolic acid, and MadA showed higher binding energy scores, and these can be considered as lead compounds for more research into their potential as treatments for vascular dementia [67, 68].

Celastrol:
Celastrol suppressed the expression of BACE-1 and blocked NFκB activation in a dose-dependent manner. By decreasing β-cleavage of APP, celastrol effectively reduced the formation of Aβ1-40 and Aβ1-42, resulting in lower levels of APP-CTFβ and APPsβ. Additionally, after a long-term course of celastrol, the brains of Tg PS1/APPsw showed a decrease in Aβ plaque burden and microglial activation [69]. Celastrol may help prevent learning and memory loss brought on by intrahippocampal Aβ25-35 by promoting synaptic growth, preserving hippocampal energy metabolism, and reducing inflammation [70]. One intriguing treatment option for AD is celastrol cause TFEB (transcription factor EB) agonist [71, 72]. One of the studies showed that celastrol can reduce MI and enhance cognitive function in a number of preclinical studies, indicating that it could be used as a natural lead chemical to create a new neuroprotective drug [73]. One study showed that there are lines of evidence supporting the therapeutic potential of celastrol in both in vitro and in vivo settings for amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cadmium-induced neurodegeneration, Alzheimer's and Parkinson's diseases, and psychiatric conditions like depression and psychosis [74].

Pristimerin:
Prismerin inhibited the MKK7/JNK/AP-1 and IKKα/β/NF-κB signaling pathways in LPS-activated BV-2 microglia by decreasing the expression and interaction of TNF Receptor-Associated Factor 6 (TRAF6) and Interleukin-1 Receptor-Associated Kinases (IRAK1), thereby limiting TGF-beta activating kinase 1 (TAK1) activation. For the treatment of neurodegenerative illnesses brought on by hyperactivated microglia, pristimerin may be a novel therapeutic drug [75]. Pristimerin's ability to reduce inflammation has been linked to the NOD-like receptor protein 3 (NLRP3) inflammasome, a cytosolic protein complex. Pristimerin may be useful in treating AD since it decreased NF-κB, TNF, and ROS [76, 77, 78, 79].

Oleanolic acid:
Numerous diseases can be prevented by the antioxidant qualities of oleanolic acid (OA). However, it has an impact on oxidative stress by increasing the expression of uncoupling protein-2 (UCP2) and stanniocalcin-1 (STC-1) in N2a/APP695swe cells. The function and mode of action of OA in oxidatively stressed N2a/APP695swe cells were investigated here [80]. Additionally, without changing BDNF levels, OA decreased the phosphorylation of ErbB4 and TrkB and increased the production of GDF11. Therefore, OA may offer a new and potential treatment approach for AD patients by preventing oxidative stress, ferroptosis, autophagy deficiencies, mitochondrial damage, and ER stress, thereby shielding neurons from APP-induced neurotoxicity [81]. In SH-SY5Y cells exposed to oxygen-glucose deprivation/reoxygenation (OGD/R), OA reduced cytotoxicity and excessive intracellular reactive oxygen species (ROS) by controlling the glycogen synthase kinase-3β (GSK-3β)/heme oxygenase-1 (HO-1) signal as well as MAO-B, P-gp, GSK-3β, and CD14. Furthermore, OA treatment dramatically decreased the neurological scores and the extent of cerebral infarction in the rat models of cerebral ischemia with middle cerebral artery blockage (MCAO) [82, 83].

Tarexerol acetate:
Taraxerol's anti-inflammatory effects can be attributed to its molecular mechanism and interactions with a variety of molecular targets, such as COX, MAPKs, and NF-κB [84]. Taraxerol can exercise its anti-inflammatory effects through a molecular process that involves interactions with a variety of molecular targets, such as COX, MAPKs, and NF-κB. The neuroprotective action of taraxerol in neurodegenerative illnesses such as AD [65, 86, 87].

Asiatic acid:
Asiatic acid cytotoxicity assay and internalization studies were assessed in SH-SY5Y cells, and thioflavin T (ThT)-treated Aβ 1–42 cells were assessed for additional neuroprotective effectiveness on intracellular amyloid beta (Aβ) aggregation. After assessing the behavioral acquisition effects in a unilateral, intracerebroventricular AD model produced by Aβ1-42, the histopathology and neurotransmitter level quantification were reveal the neuroprotection [88]. Asiatic acid regulates PI3K/Akt/GSK-3β signaling to shield differentiated PC12 cells from tau hyperphosphorylation and Aβ25–35-induced apoptosis. Asiatic acid also protects neurons by acting through the cholinesterase pathway [89, 90, 91].

betulinic acid:
Ursolic acid (UA), betulin (B), and betulinic acid (BA) are pentacyclic triterpenoid chemicals that have a range of biological actions, such as anti-inflammatory,

neuroprotective, and antioxidant qualities. This review focuses on the potential molecular mechanisms and therapeutic efficiency of triterpenoids in preventing neuronal damage and regaining cognitive function in neurodegenerative illnesses [44, 92].

Bartogenic acid:
To ascertain the effects of an extract of Barringtonia racemosa seeds, mice with amyloid beta (Aβ)-induced neurodegeneration had their brains studied. The development of AD and other dementias is accelerated by the neurotoxic effects of amyloid beta peptide (Aβ25–35) buildup. rise in IL-10 and a fall in proinflammatory indicators. BRSE has been shown to enhance cognition through regulating neuro-immune function and neuro-inflammation. Stress reduction is controlled by the hypothalamicpituitary-adrenal axis, which also regulates both of these processes. The study's findings imply that BRSE could be useful in the treatment of AD [93].

Tormentic acid:
One of Potentilla chinensis's main active ingredients, tormentic acid (TA), has been shown to have anti-inflammatory qualities. It is uncertain, therefore, how TA can affect AD memory loss and neuro-inflammatory reactions. The current study examined the therapeutic impact of TA on AD mice's learning and memory impairment as well as neuro-inflammation. In BV2 cells exposed to Aβ, TA inhibited the nuclear translocation of nuclear factor-κB (NF-κB) p65 and the generation of pro-inflammatory markers. In a neuron-microglia co-culture system, TA also enhanced neuron survival and decreased inhibited neurotoxicity [94]. Tormentic acid protect CNS via the activation of PI3-K/Akt/GSK3β, Wnt/Î²-catenin signalling also activating the liver X receptor alpha [95, 96, 97].

Glycyrrhetic acid:
The potent antioxidant properties of 18β-Glycyrrhetinic acid, a triterpenoid aglycone of glycyrrhizin, have been documented. It has the ability to inhibit voltage-gated sodium channels, inhibit cholinesterase, and inhibit BACE1 both in vitro and in silico. With these mechanism it helps to treat Alzheimer's [98, 99, 100, 101].

Corosolic acid:
Pro-inflammatory enzyme that catalyzes the hydrolysis of membrane phospholipids into lysophosphatidic and arachidonic acid, which are the building blocks for the synthesis of numerous pro-inflammatory mediators, including prostacyclins, prostaglandins, thromboxanes, leukotrienes, and platelet activating factors, which take part in invasion, migration, metastasis, and proliferation can be prevented by Corosolic acid [102, 103, 104].

23-Hydroxy butulinic acid:
In the rat model of Parkinson's disease, betulinic acid influences molecular alterations, pain, anxiety, and motor dysfunctions via an antioxidant mechanism [105]. While iron chelation activity was evaluated using ferrozin, betulinic acid's antioxidant capacity was ascertained utilizing superoxide dismutase (SOD) and catalase assay kits. The granuloma rat model generated by cotton pellets was used to assess anti-inflammatory efficacy. Cyclooxygenase (COX) activity was assessed using COX kits, while anti-acetylcholinesterase (ACHE) research for neuroprotection was conducted using an acetylcholine kit [106]. PI3/AKT/mTOR, TNF-alpha/NF-kappa B, JNK-p38, HIF-α/AMPK, and Grb2/Sos/Ras/MAPK are among the signaling pathways that betulinic acid affects and which initiate their diverse biological actions for neuroprotection [107].

Euscaphic acid:
Esophic acid has a special anti-AChE effect. It also act through antioxidant potential to exert the neuronal protection [42, 48, 108].

Ursolic acid:
Recent research indicates a correlation between ursolic acid and the clinical hallmarks of AD (AD) and reduced adult neurogenesis, which is essential for maintaining synaptic plasticity and hippocampus functioning as well as synaptic control. According to these findings, substances that enhance neurogenesis and mitigate cognitive and synaptic regulatory deficiencies must be developed [109]. AChE activity was suppressed by ursolic acid in a dose-dependent manner that was both competitive and non-competitive. Exogenous transgene transcription and expression levels were unaffected by ursolic acid. Protease activity was increased in vivo and the ubiquitin-proteasome system was transcriptionally elevated by ursolic acid. However, the therapeutic effect of ursolic acid on behavioral paralysis was eliminated by the proteasome inhibitor MG132, and the therapeutic effect of ursolic acid was dependent on Parkinson's disease [110, 111, 112].

Ceanothic acid:
Ceanothic acid inhibited AChE activity in a dose-dependent manner. Ursolic acid had no effect on the transcription or expression levels of exogenous transgenes. In vivo, protease activity rose [113]. In a dose-dependent manner, ceanothic acid inhibited AChE activity. Ceanothic acid had no effect on exogenous transgene transcription or expression levels. Increased protease activity in vivo may help reduce Tau hyperphosphorylation caused by ceanothic acid [114, 115].

Lupenol:
It is a pentacyclic triterpenoid that has a broad spectrum of biological. uses. It can be found in fruits, vegetables and medicinal plants. It has demonstrated increased permeability of the blood-brain barrier as well as potent anti-inflammatory and antioxidant qualities. Lupeol's binding and inhibitory properties have also been studied and shown to be successful against specific AD receptor proteins and enzymes. With oxidative stress it affect amyloid plaque [116, 117].

Conclusion:

The class of multifunctional natural chemicals known as pentacyclic triterpenoids and their semi-synthetic derivatives can inhibit AD-induced neuronal degeneration. Due to their interactions with various biomolecules, these chemicals have a wide range of effects. Their widespread consumption by all populations across the globe attests to their safety. The central focus of the current study is systematic research on the Pentacyclic triterpenoids and derivatives play a multifunctional role in AD' treatment. By interacting with targets molecular such as free radical scavenging, nuclear factor kappa B (NF-κB), protein kinase C (PKC), nuclear factor erythroid-derived like 2 (NrF2),such a s nuclear factor erythroid-derived like 2 (NrF2), nuclear factor kappa B (NF-κB), protein kinase C (PKC), free radical scavenging, TNF-α, IL-1β, Promote neuronal cell growth, Inhibition of acetylcholinesterase, suppression amyloid plaque and pentacyclic triterpenoids have also been demonstrated to produce neuroprotective effects and treat AD.

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