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Review Article

Herbal Drug Development for Alzheimer's Disease: A Promising Approach through Computer-Aided Drug Design

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ABSTRACT

Dementia has arisen as a severe worldwide health concern in recent decades as the world's population ages. The most frequent kind of dementia is Alzheimer's Disease (AD). Despite substantial medication and developmental research, there are just a few FDA-approved medications for Alzheimer's disease. Alternative methods to AD therapies are urgently needed since existing medicines merely give symptomatic alleviation and are usually linked with side effects. A number of medicinal plants have been identified as nootropics, which increase mental and cognitive capabilities by influencing various brain physiological pathways. *In silico* methodologies, often known as Computer Aided Drug Design (CADD) investigations, are becoming more popular in industry and universities. They include a thorough grasp of molecular interaction from both a qualitative and quantitative standpoint. These approaches create and modify 3D molecular structures, distinct molecular attributes, and compute descriptors then design models, and use other computing drug research tools. The molecular structure of a system may be analyzed to extract useful information and forecast the potential of bioactive chemicals. This review focuses on *in silico* screening of certain phytochemicals which can be found beneficial in Alzheimer's disease.

Keywords: Alzheimer's disease, Alkaloids, Flavonoids, Terpene.

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INTRODUCTION

Alzheimer's Disease (AD) is an unalterable neurological illness that causes memory, behavior, visual-spatial perception, language, speech, cognition, and everyday functional activities to deteriorate over time, ultimately leading to death and dementia. Extracellular senile intracellular Neurofibrillary Tangles (NFT) and Neuritic Plaques (NP) are hallmarks of Alzheimer's Disease (AD)[1] and may be seen in the brain parenchyma and brain arteries.[2] Synaptic and neuronal function is disrupted, dendritic arborization are removed, and neurotransmitter levels are reduced, all of which contribute to gradual loss of neurons and brain capacity.[3] Figure 1 contrasts the characteristics of a healthy brain to those of an AD patient in the advanced stages of the disease.

Neuritic plaques are beta-amyloid (A) protein aggregations (10–160m in diameter) surrounded by dead neurons, apolipoprotein E, astrocytes, microglia, proteoglycans, and α-1-antichymotrypsin.[4] Three endoproteases, α-, β- and γ-secretase,[5] sequentially degrade Amyloid Precursor Protein (APP) to create Aβ peptides of various lengths.[6] The primary isoforms of Aβ in plaques have become recognized to be Aβ1-42, Aβ4-42, and Aβ1-40.[7] According to the amyloid cascade theory, AD is caused by mutation in PSI, PSII, and APP genes that cause preferential APP cleavage, resulting in the formation of a longer variant of A peptide. These peptides have a propensity for forming sheets, which then clump together to create neuritic senile plaques surrounding neurons in brain tissue, resulting in synaptic damage and dendritic loss. Neuronal degradation and death occur as Alzheimer's disease advances, resulting in dementia and other signs.[8]

The major component of intra-neuronal NFTs is tau protein, which is arranged in hyperphosphorylated paired helical strands.[9] This has been hyperphosphorylated self-assembles into intermediate aggregates, coupled helical filaments, and NFTs.[10] Due to the destabilization of the neuronal cytoskeleton, hyper-phosphorylation of this protein interrupts its normal activity in regulating vesicle-axonal transport, resulting in the loss of dendritic spines and the accumulation of neurofibrillary tangles, as well as toxic species of soluble tau, causing oxidative cytotoxicity, neurodegeneration, and inflammation.[11]

In Alzheimer's disease, reactive oxygen species cause oxidative stress. Neurodegeneration is caused by oxidative stress, which causes free radical attacks on brain cells. However, O_2 is

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necessary for life, an unbalanced metabolism and excessive production of Reactive Oxygen Species (ROS) lead to various illnesses, like Parkinson's disease, AD, ageing, and a variety of other neurological illnesses. The histological and experimental data supporting the role of oxidants in the etiology of AD (oxidative-stress-hypothesis) is growing all the time.[12]

One of most noticeable alterations in brains of Alzheimer's disease patients is a drop in hippocampal and cortical amount of the Acetylcholine (ACh) as disease progresses. On the behavioral side, a significant reduction in ACh levels impair cognitive performance.[13] In several cholinergic routes in the peripheral and central nervous systems, AChE is engaged in the cessation of impulse transmission via fast hydrolysis of the neurotransmitter acetylcholine. Various inhibitors cause enzyme inactivation, which results in acetylcholine buildup, hyperstimulation of muscarinic receptors and nicotinic, and disruption of neuro-transmission. As a result, AChE inhibitors[14] are used as relevant medications and poisons because they interact with the enzyme as their principal target.

This disease is progressive, which means that symptoms arise gradually and increase as time passes.[15] Stages of Alzheimer's disease development have been defined based on suspected brain alterations and associated clinical changes.[16] The alterations in the brain that cause Alzheimer's disease may start 20 years or more before symptoms manifest.[17] Scientists refer to the period of time between the onset of AD and the onset of symptoms in advanced AD as the "continuum" of the disease. Despite these brain alterations, the person may operate properly at the start of the continuum. The brain's ability to adjust for neuronal injury has reached its limit which has happened as the person progresses along the continuum, and cognitive function begins to deteriorate. Afterwards, the death and damage of neurons is severe enough that the person exhibits clear signs of cognitive impairment, such as memory loss or confusion about time and location. Basic body processes such as swallowing become affected later, leading to death.[18,19]

Synaptic plasticity and memory function are both controlled by the N-methyl-D-aspartate (NMDA) receptor. Extra glutamate may be produced from injured cells in Alzheimer's disease, resulting in persistent calcium overexposure, which may accelerate cell destruction.[20]

Mitochondrial failure, oxidative stress, and reduced metabolism may all be linked to neurodegenerative diseases, like normal brain ageing.[21] According to system biology, effective therapy of complex illnesses like Alzheimer's and cancer necessitates the restoration of broken disease networks, which often necessitates the simultaneous manipulation of numerous proteins (targets)/pathways.[22] As a result, addressing numerous pathways might result in effective and useful treatment options for AD.

The restricted number of FDA-approved medications that are frequently used has made treating Alzheimer's disease difficult. Furthermore, these medications treat AD symptomatically, offering temporary comfort rather than treating the illness by improving its pathophysiology, and have been linked to a variety of side effects. As a result, there is a pressing need to create new anti-drugs.[23]

Plant-based therapies for treating health problems have lately sparked a lot of attention, despite the fact that they have been utilized by humans since last many centuries. This old traditional practice of employing medicinal plants has resulted in a large body of anecdotal data demonstrating the safety and usefulness of several species. As a consequence of secondary metabolism, medicinal plants provide an infinite variety of chemicals, resulting in more chemical diversity than other natural sources. For AD medication development, researchers have demonstrated a keen interest in exploring historically used medicinal herbs, their compounds, and even their combinations.[24]

Computer Aided Drug Design (CADD) is based on the assumption that pharmaceutically active chemicals interact with macro-molecule targets, most often nucleic acids or proteins. The steric complementarity of contacting surfaces of molecules, hydrophobic interactions, electro-static force, and the creation of hydrogen bonds are all important elements in such interactions. These parameters are mostly evaluated during the study and prediction of two-molecule interactions.

Flavonoids

Several scientific investigations[25,26] have shown that polyphenols have beneficial properties. Their most apparent and simple activity is to reduce cell damage induced by free radicals, which has also been detected in Alzheimer's disease.[27,28] Rodacka *et al.*[29] discovered that the polyphenols resveratrol and tiron had neuroprotective effects through inactivating Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) produced by superoxide anion radicals. The docking of both ligands with the enzyme demonstrated that the radical's resveratrol and tironare more effective than the superoxide anion alone in inactivating glyceraldehyde-3-phosphate dehydrogenase, with tiron being the greater antioxidant.

Utilizing examples from earlier scientific investigations using water extracts, Lakey-Beitia *et al.*[30] demonstrated that extracts from *Caesalpinia crista* leaves inhibited Aβaggregation from monomers and dissolved preformed Aβfibril.[31] *Ginkgo biloba* extract decreased oligomer formation,[32] *Centella asiatica* decreased synuclein aggregation,[33] and *Paeonia suffruticosa* extracts decreased A fibril production while also destabilizing preexisting amyloid fibrils.[33] He hypothesized that polyphenols may modify APP processing, inhibit Aβ aggregation and inhibit fibrils. Polyphenolic glycosides like rutin, apigenin, and

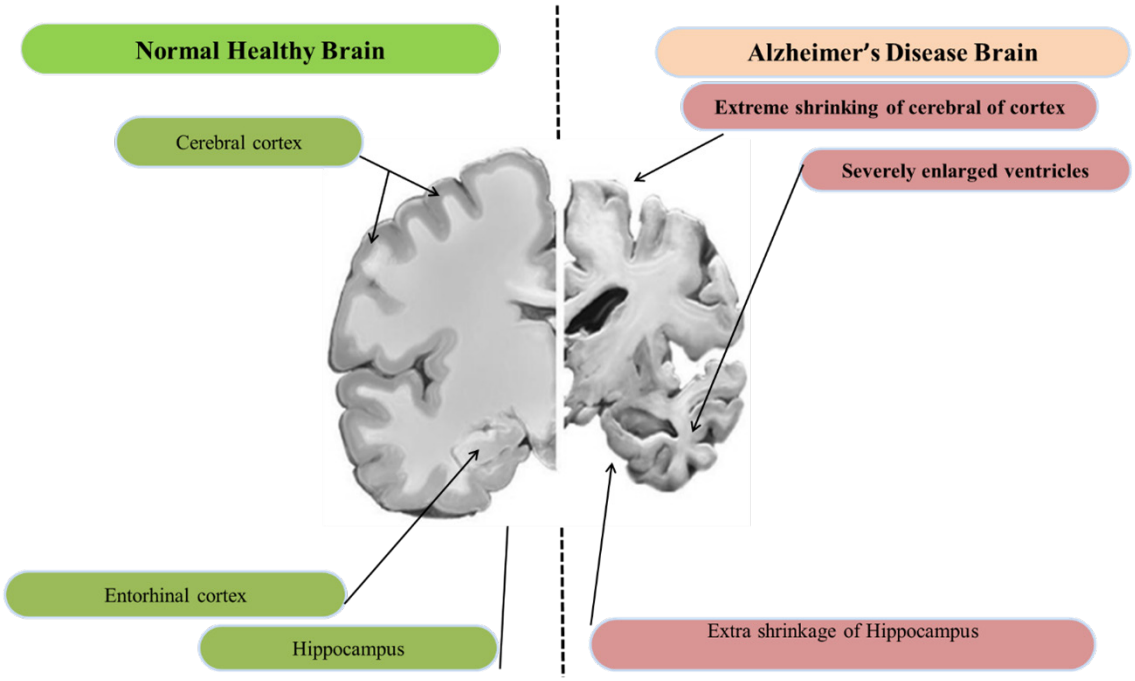

Figure 1: Anatomical changes in Normal brain vs Alzheimer's brain.

naringenin, according to Mora-Pale *et al.*,[34] inhibit -amyloid aggregation.

Wang *et al.* 2012[35] investigated Mangostin, a polyphenolic xanthone produced from *Garcinia mangostana* Linn. This molecule has been used in various investigations[36,37] and has been found to exhibit membrane-protective,[38] anti-malarial,[39] anti-viral,[40] anti-bacterial,[41] and other actions.

Tau proteins are the main components of glial fibrillar and intra-neuronal lesions in AD, which cause dementia and accelerate the neuro-degenerative process. Madeswaran *et al.*[42] used molecular docking to investigate the tau protein kinase I inhibitory effect of six flavonoids. Catechin, acacatechin, scopoletin, galangin, memantine, and silbinin were the chemicals studied. Lipinski's rule was used to compute and assess parameters such as molecular weight, molecular formula, rotatable bonds, aromatic carbons, and the number of torsions. The lowest energies were found in galangin and silbinin, which might be employed in future research to treat Alzheimer's disease.

Six flavonoid compounds derived from the local medicinal plant *Rhus parviflora* (Anacardiaceae), quercetin-3-O-b-D-galactopyranoside, sulfuretin, ureusidin-6-O-b-D-glucopyranoside, aureusidin, cupressuflavone, and hovetrichoside C were shown to be CDK inhibitors in research by Shrestha *et al.*[42] Molecular docking was used to test the chemicals. CDK5/p25 three-dimensional structures were retrieved from the RCSB protein data bank, while produced flavonoid compounds structures were chosen from the National Center for Biotechnology Information's Pubchem chemical database. Through hydrogen bonding with active-site residues at GLN130 and CYS83, all of the flavonoids demonstrated excellent interactions with the receptor. Aureusidin and auroras, on the other hand, yielded higher energy values.

The top-class of medications used to cure AD were acetylcholinesterase inhibitors. Most often used AChE inhibitors, such as tacrine and physostigmine, have shown certain issues in clinical investigations, including difficulty with hepatotoxic potential and oral administration. The discovery of donepezil hydrochloride, which launched a new class of acetylcholinesterase inhibitors with longer and more selective action and tolerable side effects, was the result of research aimed at finding a new kind of acetylcholinesterase inhibitor. Sugimoto and coauthors used CADD investigations to find novel inhibitors, such as QSAR-3D, Comparative Molecular Field Analysis (CoMFA), and docking. Because there is a negative connection between IC_{50} and DE, QSAR modelling on the benzamine set shows that the cis isomers of the molecule have a higher intrinsic activity than the trans isomers (C-T).

As AChE inhibitors, researchers are now using secondary metabolites such as flavonoids, alkaloids, and xanthones. Yang and colleagues, for example, produced a series of aporphine alkaloid analogues. Ellman's technique (modified) was used to determine the anti-acetylcholinesterase activity of the produced compounds, as detailed in the work published in 2012. Molecular docking was used to find two highly active molecules (nuciferine derivatives) that interacted as ligands with the acetylcholinesterase site: 1, 2-dihydroxyaporphine and dehydronuciferine.[43,44]

In AD, alterations in the cholinergic system are a key source of worry. The substrate is the most significant distinction between

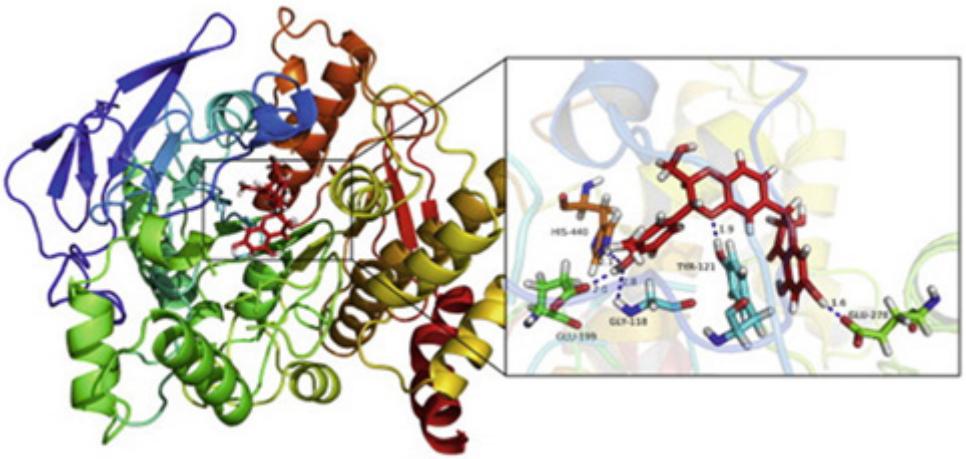

Figure 2: The combined conformation of the Aβ-silibinin complex shows that silibinin binds to the active sites of AChE.

the two cholinesterases: AChE hydrolyzes acetylcholine in the brain synapses and blood, while butyrylcholinesterase hydrolyzes Butyrylcholine (BChE) in the liver.[45-47] Two forms of cholinesterase's breakdown acetylcholine, therefore inhibiting these both enzymes with a dual inhibitor could result in increasing the acetylcholine levels in the brain and improved therapeutic effect. Drug candidates such as rivastigmine, physostigmine, velnacrine, donepezil and tetrahydro aminoacridine (tacrine) are being studied as AChE inhibitors.[48,49]

A most common pathological feature of ADis Amyloid plaques in the brain.[50] A 39–43 amino acid peptide, the amyloid-peptide (A), is the plaques' most important protein component. A deposition produces Reactive Oxygen Species (ROS), that are implicated in the neurodegenerative and inflammatory pathophysiology of AD.[51,52] The amyloid-peptide (A) produced by proteolytic cleavage of Amyloid Precursor Protein (APP) by - and -secretases is a key component of amyloid plaques. Many writers ascribe cognitive decline to the deposition of amyloid plaque, which is a hallmark of Alzheimer's disease, although there is a suggestion that plaque production is a result of metabolic deterioration in AD patients' brains.[53] According to recent research, Acetylcholinesterase (AChE) may increase formation of amyloid fibril by interacting with the PAS of acetylcholinesterase, which gives stability to the acetylcholinesterase-A complex. This is more hazardous than single A peptides alone.

Utilizing a spectrophotometric approach, Li *et al.*[54] investigated various compounds against both cholinesterases, utilizing galanthamine and tacrine as reference compounds. Using curcumin as a reference, aggregation inhibition, self-induced kinetic ChE inhibition, and metal-chelating activities were investigated. An isolated compound showed to be the most powerful AChE inhibitor in these tests, thus the authors molecular docked it with TcAChE id PDB: 2ckm. Through - contacts with distances of 4.24 and 5.05 A, the flavonoid ring interacted between the indole ring of Tyr70 or Trp 279. Despite the fact

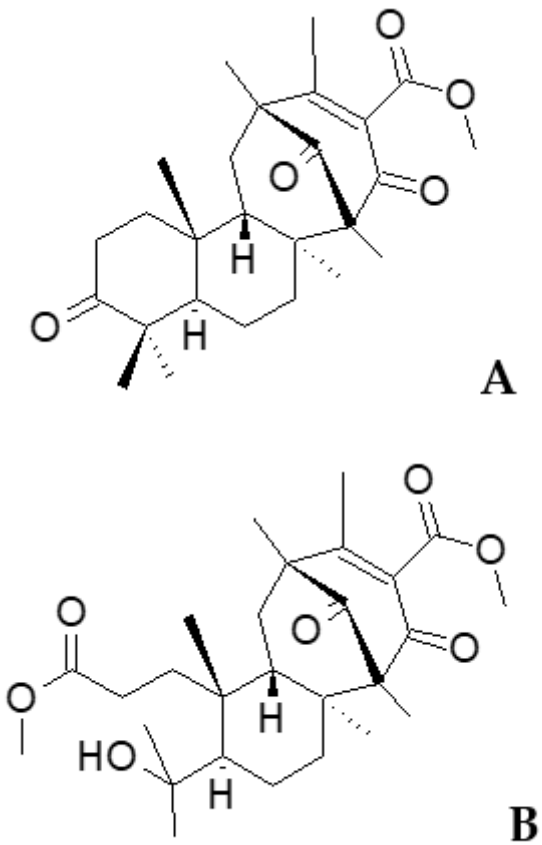

Figure 3: (A, B) Asperterpenes.

that 13 s is a powerful inhibitor, 13 k has more multipurpose capabilities.

Much research on multifunction anti-drugs Alzheimer's have been published, with some of them employing natural compounds.[55-57] Lou *et al.*[58] synthesized and tested 17 4-dimethylamine flavonoid derivatives for their anticholinesterase,

anti-A aggregation, and anti-ROS properties. The scientists used two enzymes from the Protein Data Bank to analyse the ligands, in this investigation π-π interactions were also discovered in the residue Trp 279. The findings revealed inhibitory potentials for both BChE and AChE that were comparable to or better than rivastigmine.

To clarify the structural characteristics of flavonoid by products which contribute to the inhibitory action of acetylcholinesterase, Goyal *et al.*[59] used pharmacophore-based virtual screening and 3D Quantitative Structure-Activity Relationship (QSAR) to study 24 flavonoids. Using comprehensive docking experiments, the binding mechanisms of action with the enzyme were examined using a QSAR-3D model. Two aromatic rings, one hydrogen-bond acceptor, two hydrophobic region, and were the best pharmacophore hypotheses. 4 lead compounds were identified as a result of this research, one of which was shown to be particularly effective in inhibiting the dual AChE-binding site.

Chakraborty *et al.*[60] used QSAR models to evaluate polyphenols' anti-amyloidogenic effects. CODESSA was given eighteen chemicals to calculate quantum chemical and thermodynamic descriptors for electrostatics, geometrical, quantum chemical, topological, constitutional, and thermodynamic properties. The best QSAR model was then used to create a database of 200 phytochemicals. This strategy is used to find fresh leads.

Morin is a flavonoid that has been shown to have anti-aggregation properties in Aß monomers and dimers[61] as well as inhibitory properties in the enzyme AChE.[62] Morin's hydrogen-bonding capacity and aromaticity, hydrophobicity were detected in molecular dynamic simulations, and these properties may influence binding energies. Morin has an effect on A's tertiary and quaternary structure. Morin's AChE inhibition was explored using molecular docking, much as galangin, myricetin, fisetin, and quercetin. The structure activity correlations were then constructed by Remya and associates.[63]

A flavonoid silibinin, derived from *Silybum marianum*, was investigated to see whether it may be utilized for the treatment of AD. It acts as a dual inhibitor of acetylcholinesterase and peptide aggregation. The researchers investigated the affinity of silibinin with Aβ and acetylcholinesterase *in silico* using molecular dynamics and docking simulations.[64] The flavonoid connects with the active sites of acetylcholinesterase in Figure 2.

Alkaloids

Alkaloids are N-containing heterocyclics that are found in a variety of plant species. The majority of alkaloids are hazardous (including nicotine, strychnine, morphine, ephedrine, quinine), but researchers have found bioactive,[65] including fungal infection treatment,[66] anti-malarial,[67] anti-HIV,[68] and inhibition of AChE in Alzheimer's disease.[69-72]

The isoquinoline, quinolizidine, triterpenoidal/steroidal, and indole classes of Amaryllidaceae, Lycopodiaceae and Buxaceae are regarded major alkaloid inhibitors of BChE and AChE, according to Konrath *et al.*[73] They are described in terms of their structural variety and physico-chemical qualities, with a focus on SARs and docking investigations. The researchers demonstrate that a positively charged nitrogen interacts with one of the AChE-binding sites.

Another enzyme linked to Alzheimer's disease is Retinoblastoma-associated protein (RbAp48), which causes memory loss when deficient. Huang *et al.*[74] used Perivine, eicosandioic acid, and bittersweet alkaloid II from traditional Chinese medicine in docking investigations.

Makowska *et al.*[75] used molecular docking and hydrophilic interaction liquid chromatography to investigate trigonelline's affinity for the A(1–42) peptide. Trigonelline is associated with the His 6, 13 and 14, and Tyr10 residues in the A(1–42) protein, according to the researchers.

The alkaloids 3-epimacronine and lycoramine found in *Zephyranthes carinata* plant have been shown to inhibit BChE and AChE may be useful for the treatment of AD. Cortes *et al.*[76] discovered that 3-epimacronine derivatives were selective AChE ligands in a docking investigation. Analytical experiments utilising GCMS and an assay evaluating inhibition of acetylcholinesterase activity revealed that alkaloids generated by other species in Amaryllidaceae family also inhibit BChE and AChE.[77-80]

The Apocynaceae family's Holarrhena anti-dysenterica has a long history of usage in medicinal purposes, and its alkaloids have been shown to have anti-malarial, anti-bacterial, anti-gastro intestinal, and anti-cancer disease properties.[81-84] Yang and colleagues[85] looked examined conimin, conarrhimin, conessimin, isoconessimine, and conessine, which were all isolated from H. anti-dysenterica. The inhibitory action of AChE was investigated *in vitro*, and the authors used the data to create a SAR model. Docking with the enzyme was used to test the compound. The amount of methyl groups in a ligand improved its ability to inhibit AChE, and all ligands interacted with the protein's hydrophobic pocket.

Ul-Haq *et al.*[86] investigated physostigmine analogues although the alkaloid physostigmine inhibits AChE,[86-91] it has a short, varied bio-availability, half-life, and minimal clinical efficacy. The compounds were chosen from studies based on their AChE inhibiting activity IC_{50} values (9.78–20893.1nM); the IC_{50} values were transformed to pIC_{50} values ($logIC_{50}$). The researchers employed 32 alkaloids for the training set and eight for the test set, and they were separated into two groups: alkyl and phenyl chains and ionizable nitrogen of the morpholine moiety. The energy minimization of compound structures was utilised to construct 3DQSAR (PLS regression analysis), CoMFA and CoMSIA models. The physostigmine analogues' steric and

electrostatic potentials, as well as their atomic co-ordinates, charges, physico-chemical properties (electrostatic, hydrophobic, steric, and hydrogen bond acceptor and donor) were evaluated using these tools. The models demonstrated significant predictive abilities as well as structure-activity correlations, facilitating and encouraging the use of these substances in the treatment of Alzheimer's disease.

Terpenoids

Dimethylallyl Pyrophosphate (DMAPP) and Isopentenyl Pyrophosphate (IPP) are the two major precursors for monoterpenes, polyterpenes, diterpenes, sesquiterpenes, tetraterpenes, and triterpenes. Which are subclassified by their structure: monoterpenes, sesquiterpen Despite the range of classes, these natural products are said to include a large number of chemicals and have a variety of beneficial effects,[92-95] including anti-disease Alzheimer's;[96-99] rational planning is not required.

A marine natural substance, furano-sesquiterpene palinurin, was isolated by Bidon-Chanal *et al.*[100] Its inhibiting impact on glycogen synthase kinase 3b was discovered by the researchers (GSK-3b). The enzyme under investigation might be used to treat AD, neurological illnesses, myocardial ischemia, and cancer.[101-104] The team identified two pockets in the receptor, one at the N-terminal lobe and second at the C-terminal lobe, as possible allosteric binding sites using molecular docking. The compound's inhibitory action is based on site binding.

Two asper terpenes derived from the culture broth of *Aspergillus terreus* were the first to be reported as potent inhibitors of BACE1. Amyloid fibril, KMO, GlpG, PSH, NMDA receptor, acetylcholinesterase, BACE1, and APOE4 were studied (Figure 3) using molecular docking with 8 important enzymes implicated in AD processes.[105] BACE1 binds to ligands with a higher affinity over the various targets. Although having lower predicted binding energies.

CONCLUSION

Alzheimer's Disease (AD) is the most prevalent form of dementia, and it is now a worldwide and economic danger. Because Alzheimer's disease is a multifactorial disease, there are a variety of treatment targets. The FDA-approved medication for Alzheimer's disease now only addresses symptoms and does not address memory issues or slow the pace of AD neurodegeneration. As a result, there is still a pressing need to find alternative methods to AD treatments that target many underlying pathways in order to improve AD therapy. Many medicinal plants may be effective in the treatment of serious illnesses such as stroke, cancer, neurodegenerative disorders, and cardiovascular problems, according to traditional medical systems. Efficacy of several active substances obtained mostly from medicinal plants in dementia, particularly Alzheimer's disease, has been studied. In reality, modern anti-medications, Alzheimer's like galantamine and rivastigmine, are phytochemical (alkaloids)-based medications that are selective, competitive AChE inhibitors that may be synthesised or derived from Galanthus sp. bulbs and flowers. Some Phyto drugs have recently been thoroughly investigated in cell culture and animal models of Alzheimer's disease, as well as in clinical studies. Extracts of *Curcuma longa, Ginkgo biloba, Angelica sinensis*, and *Withania somnifera* showed promise in the treatment of Alzheimer's disease and should be explored further to understand their maximum potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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