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(REVIEW ARTICLE)

An overview of Alzheimer's disease and therapeutic potential of natural products via *In Silico* Approach

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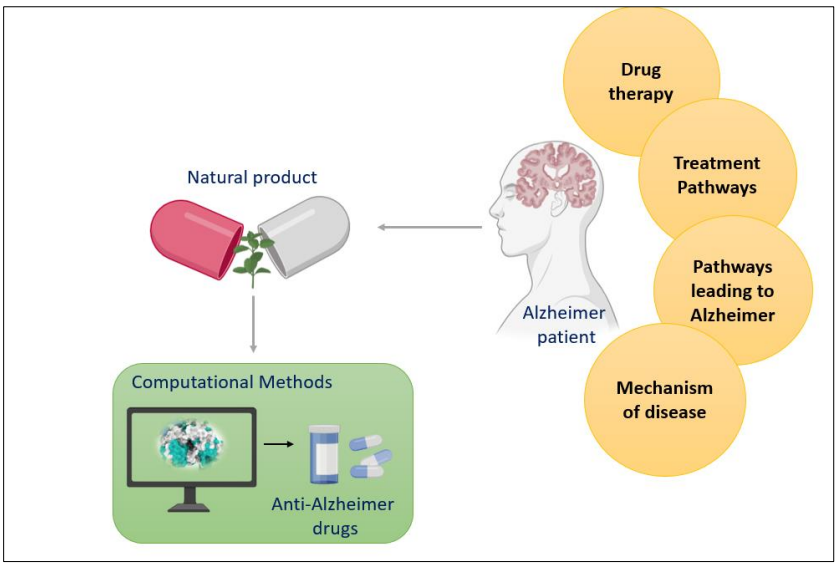
Abstract

Alzheimer's disease (AD) is a prominent neurodegenerative illness that causes perpetual loss of intellectual functioning and is a major contributor to dementia cases globally. As per epidemiological statistics, there are approximately 74.7 million AD patients worldwide. The main signs of AD are mostly forgetfulness of recent events and memory loss. In this review we focused on numerous pathways leading to AD, those are oxidative stress, synaptic loss, neuroinflammation, and accumulation of amyloid plaques and neurofibrillary tangles being the major hallmark for the pathology of AD. Natural Product has proved to be best choice of treatment for AD as they offer fewer negative effects and long-lasting advantages. However, many drugs tend to fail clinical trials so as to minimize this possibility computational methods came into light. In this study we discuss the advantages of Computational methods as they are less cost effective, time saving, speeds up the drug design process, requires less animal testing and high success rate using *in silico* ADMET predictions, molecular docking and dynamic simulation thus making it an excellent tool. This review summarizes information about Alzheimer disease mechanism and the role of natural products in treatment of AD by using *in silico* techniques.

Graphical Abstract



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Keywords: Alzheimer Disease; Natural Products; β-Amyloid; Tau Protein; Computational Methods; Molecular Docking

1. Introduction

The leading neurodegenerative disorder Alzheimer disease(AD), was first identified and coined in 1906 by Dr. Alois Alzheimer[1]. It is recognized as one of the most prevalent type of dementia since it is a progressive complex multifactorial disorder[2]. Memory loss and other cognitive impairments severe enough to interfere with daily life routine which together referred to as dementia. Cognitive impairment, behavioral changes, and gradual memory loss predominantly characterize AD.

AD is frequently classified into Early Onset AD(EOAD) and Late Onset AD(LOAD). EOAD cases can occur before the age of 65 and are both familial and sporadic, accounting for as little as <5% of all AD cases[3]. AD with an early onset affects around 110 out of every 100,000 persons aged 30 to 64. There isn't a single gene that causes early-onset Alzheimer's for the majority of people. A genetic mutation (error in a gene) or family history are two risk factors that may contribute to early onset, the genes that are responsible are Amyloid Precursor Protein (APP) or Presenilin 1 (PSEN1) or Presenilin 2 (PSEN2)[4], [5], [6]. In around 5% of cases of EOAD, a genetic mutation is responsible for this disease[7]. However, less than 1% of patients suffering from AD have one of these causative genes.

On the contrary, LOAD is more prevalent as it accounts for approximately 90-95% of all AD cases. Typically, after 65 years of age LOAD clinical symptoms get more advanced in patients[3]. Even though AD is still not fully fathomed, it is believed to be caused by an abnormal deposition of β-amyloid plaques (extracellular senile plaques) and accumulation of neurofibrillary tangles of tau protein which leads to atrophy and neuron death[8]. In AD, age is considered as the biggest risk factor. About 3% of adults age 65–74, 17% of age 75–84, and 32% of 85 years of age and beyond are affected by this condition[9], [10]. The diagnosis of AD happens once every 66 seconds, approximately 44 million people worldwide are affected by this disease or related types of dementia[11]. According to the reports, 6.7 million Americans had clinical AD in 2023; and by 2030 this number is predicted to rise to 8.5 million[12]. In another report, the estimated value reached 74.7 million worldwide, and the expense of caring for these individuals will be about US$ 2 Trillion by 2030[13]. In 2023, there was a great progression in Alzheimer's disease by 26.07% in 65-74 years, 37.90% in 75-84 years and 35.40% in 85+ years[14]. **Figure 1**. Shows the global-level schematic pie chart of AD.

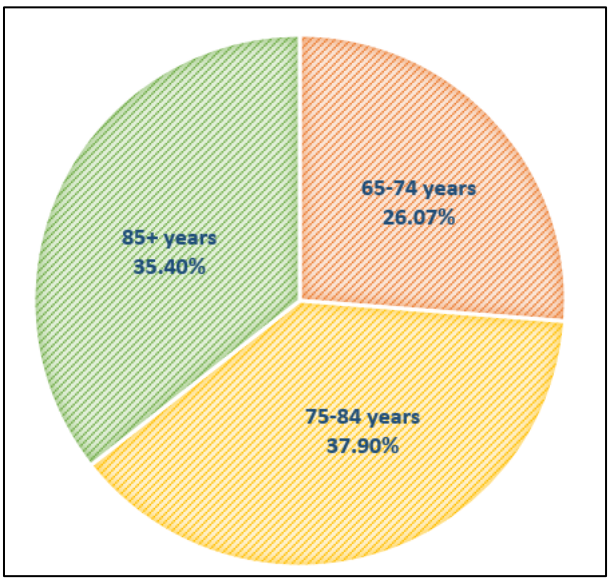

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Figure 1 Alzheimer's Disease worldwide in 2023

Currently, there is a large demand in drug therapy to gather data about the development of new pharmaceutical drugs and vaccines. These developments have produced important discoveries which improves the disease prevention, diagnosis and therapy without requiring a large amount of time and money. This review focuses on mechanism of AD and how natural products can be efficient in treatment of AD. It also explores the role of computational chemistry in this area.

2. Mechanism and Pathways of Alzheimer Disease

Alzheimer disease is generally caused by two proteins that are amyloid and tau protein. Amyloid proteins are formed around the brain cells while the tau protein forms the build up inside the brain cells. Plaques formation occurs due to the amyloid proteins while the tau proteins lead to the formation of neurofibrillary tangles[15]. **Figure 2** pictographically represents the protein mechanism.

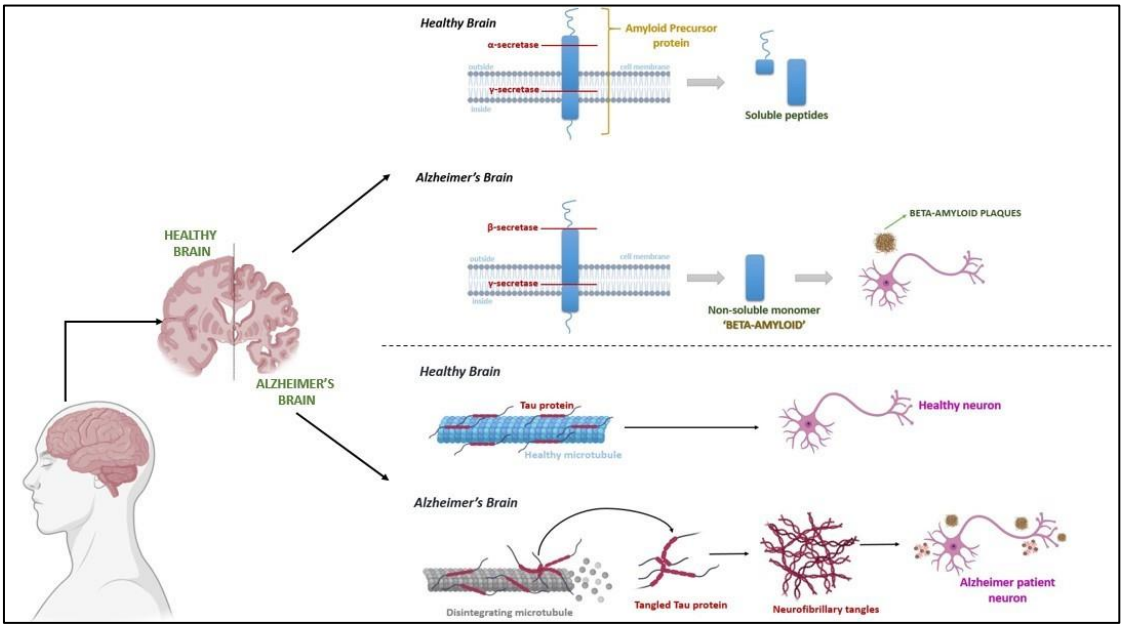

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Figure 2 Mechanism of Alzheimer Disease

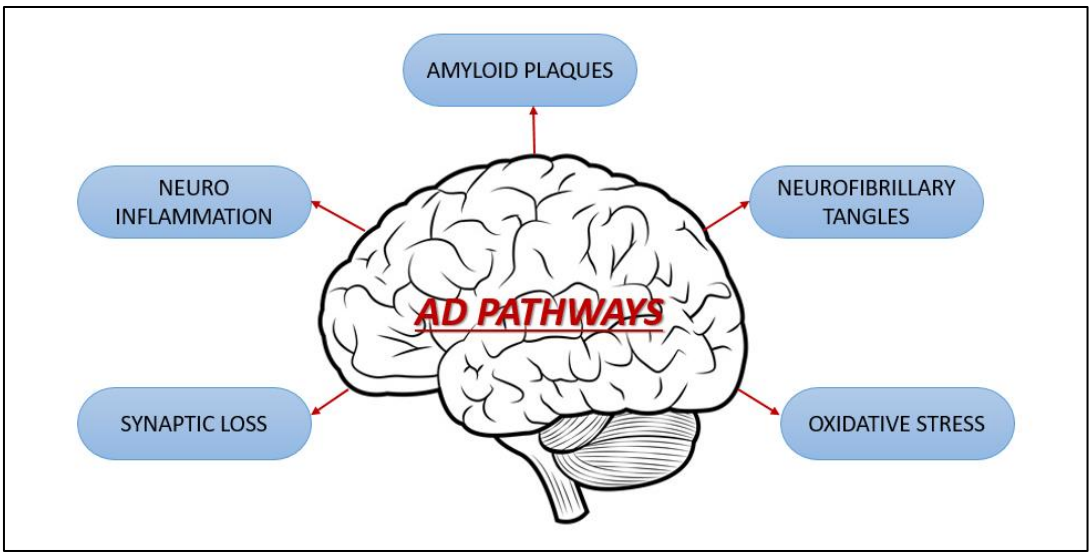

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Figure 3 Various pathways that lead to Alzheimer's Disease

These proteins influence two neural processes that causes Alzheimer. The first pathway as shown in Figure 2 involves the formation of positive lesions which are caused by the accumulation of neurofibrillary tangles and amyloid plaques. The second pathway involves the formation of negative lesions which occur due to synaptic loss. Oxidative stress, neuroinflammation and damage to cholinergic neurons are also caused by AD[16], [17]. The different pathways of AD are shown in Figure 3.

2.1. Amyloid Plaques

Amyloid plaques aka senile plaques are the main cause of AD. There are three enzymes which are primarily responsible for the breakdown of APP. Those are α-secretase, β-secretase and γ-secretase which on cleavage may result into the formation of non-soluble peptides called beta amyloid protein, or plaque[18]. The α-secretase and γ-secretase cleaves APP to form soluble peptide which are not harmful for the body. While β-secretase and γ-secretase function together, a non-soluble monomer called "amyloid beta" is formed. Because it is sticky, amyloid beta clumps together to form plaques[19], [20], [21]. These enzymes facilitate the synthesis of various amino acid fragments, comprising 43, 45, 46, 48, 49, and 51 amino acids, which finally provide Aβ40 and Aβ42. Aβ42 is considered the most toxic[2]. These amyloid plaques interfere with synaptic connection and promote inflammation, which can result in nerve damage and even amyloid antipathy, raising the risk of a brain hemorrhage[22]. The denser plaques deposition in certain parts of brain such as hippocampus, amygdala, and cerebral cortex can result into neurotoxicity, axonal and dendritic damage, synapse loss, and cognitive impairment[21], [23], [24]. The Figure 2, represents the actual mechanism of how AD is caused by amyloid protein.

2.2. Neurofibrillary Tangles

The tau proteins, which are responsible for the formation of neurofibrillary tangles, are present inside the neuron. A cytoskeleton composed of microtubules often holds neurons together. The tau proteins are members of the microtubule-related protein family, and their main function is to bind to and stabilize the microtubules[25]. However, in some pathological pathways, this phosphorylated tau results in insoluble forms, thus becoming toxic to neurons[26]. Since tau proteins are insoluble, they undergo shape changes, cease to support microtubules, and become tangled. Neurons with non-functional microtubules are unable to signal properly among themselves, leading to apoptosis[27]. Since pathological tau controls the fission proteins in the mitochondria, it damages the brain and inhibits mitochondrial function[28]. Thus, the mechanism of tau protein can be well illustrated with the help of Figure 2.

2.3. Synaptic Loss

At the early stage of AD, it is observed that synaptic damage takes place in the cortex region and limbic system leading to memory detriment[29]. The synaptic connection not only influences the basic transportation from dendrites to axons but also inhibits the transfer pathway between two neurons. It is also a contributing factor to the formation of amyloid plaques and tau protein tangles. Continual synaptic loss can result in the degeneration of dendritic spines, pre-synaptic terminals, and axons[30].

2.4. Oxidative Stress

The essential role in the pathology of Alzheimer's disease (AD) largely focuses on oxidative metabolic reactions and the production of free radicals, which primarily forms the basis of the oxidative stress hypothesis[31]. Reactive oxygen species (ROS) can react with lipids, proteins, nucleic acids, and other molecules, potentially altering their structures and functions. Consequently, tissues and organs, especially the brain, which is particularly vulnerable, can be affected by ROS due to its composition[32]. Due to oxidative stress, there is a rapid increase in chronic impairments and more central nervous system issues. Reactive oxygen species and free radicals are major contributors to AD. The brain is especially susceptible to oxidative stress due to its high oxygen consumption, which is 20% higher than other mitochondrial respiratory tissues[33]. Polyunsaturated fatty acids, which are commonly found in neurons, combine with ROS to cause a peroxidation reaction and molecular death[34].

2.5. Neuroinflammation

Neuroinflammation is recognized as a prominent factor in Alzheimer's disease (AD) and other diseases[35]. The initiation of inflammation results in persistent inflammation and nerve damage, leading to the release of other factors that trigger a chronic immune response in the brain[31]. Amyloid plaque and neurofibrillary tangle development is one of the primary causes of neuroinflammation. Genetics, obesity, a sedentary lifestyle, and diabetes are other variables that may lead to chronic inflammation, one of the features of AD[31]. This affects two types of glial cells: astrocytes and microglia, in which microglia when exposed to prolonged inflammation can cause nerve damage and atrophy[36].

3. Treatment Pathways and Drug Therapy Mechanism

AD includes two primary types of treatment those are disease-modifying therapy which slows down the disease progression and symptomatic therapy which improves cognitive function. The ongoing research hopes to produce therapeutics that target the underlying neurodegenerative processes to change the course of the disease, current treatments concentrate on improving symptoms. The medications of AD comes under two broad spectrums that are

cholinesterase inhibitors and N-methyl D-aspartate (NMDA) antagonists which focuses on treating AD symptoms[29]. In cholinesterase inhibitors, the medication works by increasing levels of cell-to-cell communication. AD is primarily caused by the reduction of acetylcholine production a chemical messenger, which is preserved by this medication[29]. Acetylcholine a neurotransmitter is mostly produced by cholinergic neurons and are associated to learning and memory formation. The degree of cholinergic depletion basically forms neuropathological hallmarks of AD. Cholinesterase inhibitors may help with behavioural symptoms including depression or agitation. This medications are administered orally or applied topically as patches[37]. Donepezil, Galantamine, Rivastigmine are commonly prescribed cholinesterase inhibitors[38].

Another effective way to treat symptoms of AD is by using N-methyl D-aspartate (NMDA) antagonists. This medication delays the onset of moderate to severe Alzheimer's disease symptoms by acting on a different brain cell communication network. NMDA plays an crucial role in both neurotoxicity and nervous system development[39]. It is also essential for synaptic transmission and synaptic plasticity which are considered as the foundation of learning and memory[40]. Recently, N-methyl D-aspartate receptor (NMDAR) activity is linked to synaptic impairment in AD[41], [42]. The main excitatory amino acid glutamate in the CNS is overstimulated when NMDARs are over-activated. This results into aberrant Ca^{2+} signaling, excitotoxicity, synaptic dysfunction, neuronal cell death and reduction in cognitive abilities. Many varieties of NMDAR antagonist have been developed but most of them have not met the criteria and have failed. In this group, Memantine is the only medication that is licensed for treating moderate to severe AD[29].

Drug treatment is a technique which combines multiple pharmaceutical drugs to treat symptoms, underlying causes or avoid disease altogether. It involves interaction with particular biological target in the body by the use of pharmacological agents also called as medications or drugs to produce therapeutic effects. The basic idea of how medications affect the body is the foundation of drug therapy. Multiple processes, including receptor binding, enzymatic inhibition, and modification of cellular signaling pathways, contribute to this interaction[43]. Globally, a substantial amount of money and effort has been dedicated for developing pharmaceutical therapy for Alzheimer's disease (AD). Many pharmacological treatments based on two established pathways are currently under development or being tested in clinical trials, focusing on the toxicity of Aβ and the abnormal hyperphosphorylation of tau in AD[44]. Drug therapy for Alzheimer's generally involves two mechanisms: the amyloid beta pathway and the phosphorylated tau pathway[44].

3.1. Amyloid Beta Pathway

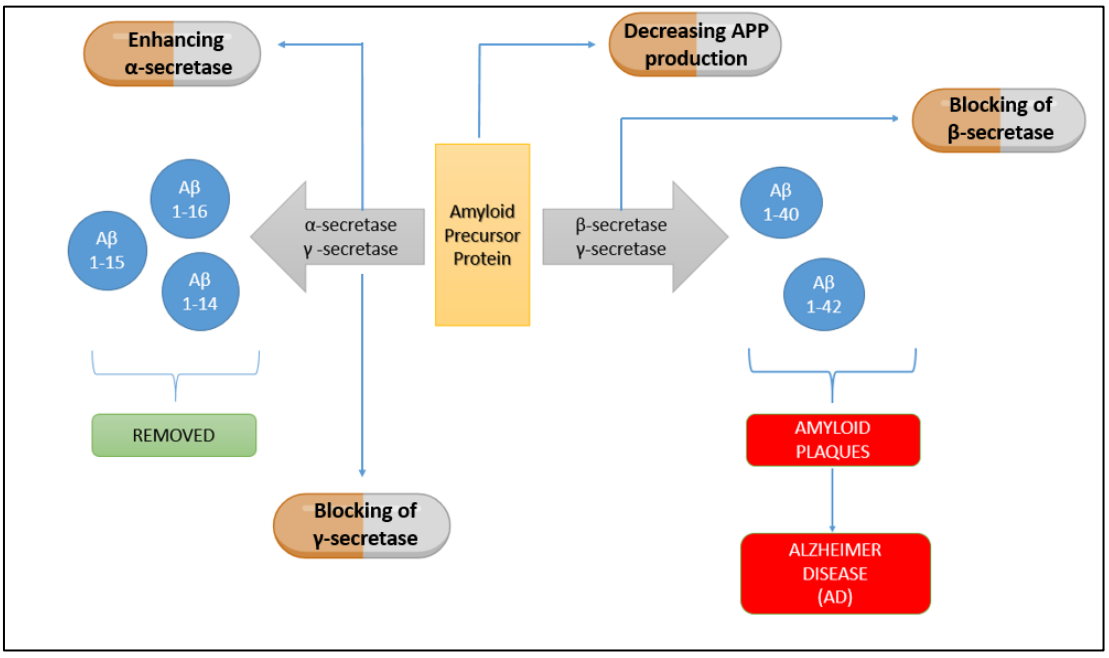

Figure 4 Amyloid Beta Pathway

Amyloid beta (Aβ) are generally produced by the amyloid precursor protein degradation[44]. This APP on cleavage with enzymes β-secretase and γ-secretase forms two components that are Aβ 1-40 and Aβ 1-42. Whereas the enzymes α- and γ-secretase cleavage results into Aβ 1-14, Aβ 1-15, and Aβ 1-16 which gets removed easily[45]. The main components of Senile plaques (associated with Aβ toxicity) are Aβ 1-40 and Aβ 1-42, which are easy to aggregate and

deposit[46]. Currently, the majority of medication development and research efforts focus on Aβ-related pathogenic processes consisting of (1) blocking β-secretase; (2) blocking γ-secretase, (3) enhancing α-secretase, and (4) decreasing APP manufacturing Figure 4. shows the amyloid beta pathway[44].

3.2. Phosphorylated Tau Pathway

Phosphorylated tau pathways as shown in Figure 5 impact microtubule activity, and abnormal hyperphosphorylation in AD patients causes neurofibrillary tangles to form[44]. It shows the presence of two important tau related kinases and phosphatases in which the first one is Glycogen synthase kinase 3 β (GSK-3β) and second is Protein phosphatase 2A (PP2A). In which, the GSK-3β is considered as the main and the most important cause of tau protein this is overcome by the help of PP2A which accounts for 70% tau dephosphorylation. Some of the methods used in medication development to reduce tau's aberrant hyperphosphorylation include the following: PP2A activity is enhanced, microtubule function is improved, p-tau aggregation is prevented, p-tau clearance is promoted, and GSK-3β activity is blocked[44].

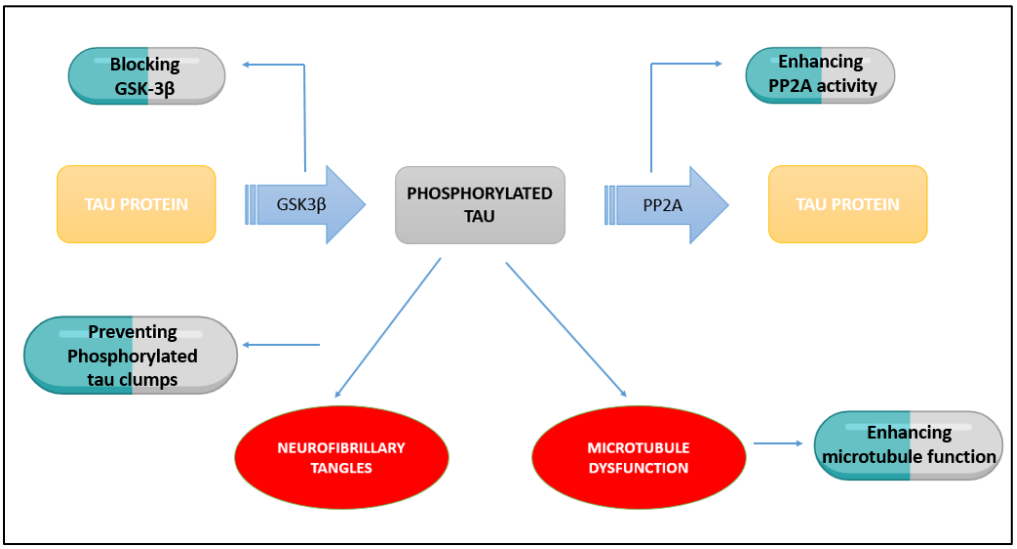

Figure 5 Phosphorylated Tau Pathway

4. Drug Therapy and the Role of Natural Product

Alzheimer disease being a non-curable disease, these drugs mainly target symptomatic treatment and slowing the disease progression. The medications of Alzheimer disease generally come under two spectrum cholinesterase inhibitor and NMDA antagonist. The some of the FDA approved drugs are Donepezil, Galantamine, Rivastigmine, Aducanumab are all used in the Alzheimer disease treatment. The results of more recent trials for two other antibodies in this class, Lecanemab and Donanemab, have demonstrated a positive and noteworthy slowing of measures for cognitive and functional decline. Since then, the FDA has approved Lecanemab in January 2023 and Donanemab in July 2024, respectively[47].

4.1. Donepezil

Another brand name for donepezil is Donepezil hydrochloride shown in Figure 6 (1). It is an AChE inhibitor that is reversible and non-competitive[48]. When treating AD, one of the best drugs is donepezil, an AChEI belonging to the second generation that is derived from piperidine[29]. It is used to treat dementia in AD patients which is defined as confusion and memory loss. The neurotransmitter that helps to transfer information in between neurons is called acetylcholine. Donepezil reduces the symptoms of dementia by effectively preventing breaking down of acetylcholine[49]. This drug is administered once per day. They are usually used to improve memory, attention, and performance of daily chores. The fact that acetylcholine is found in various areas of the body raises the possibility of unexpected adverse effects from these drugs[49]. Symptoms that are commonly seen include headaches, lightheadedness, nausea, vomiting, diarrhea, and excessive daytime drowsiness. Other significant adverse effects include yellowing of the skin, cramping in the muscles, heartburn, severe dyspepsia, stomach pain, and black stools[50]. Moreover, under some conditions, a severe allergic reaction known as anaphylaxis may also happen[51]. It is among the most affordable medications for Alzheimer's disease therapy[52].

4.2. Galantamine

Daffodil pulp is a naturally occurring source of Galantamine as shown in Figure 6 (2), one of the acetylcholinesterase inhibitors. It's administered to mild-to-moderate Alzheimer's patients[53].Additional cholinesterase inhibitor, are produce by neurons of cholinergic system which are primarily responsible for acetylcholine production. Galantamine prevents acetylcholine from being degraded in the synaptic cleft by reversibly and selectively inhibiting cholinesterase by enabling more accumulation of acetylcholine in the brain and helps in reducing the symptoms of AD[54].The oral administration is done in the dosage form of 4mg/ml oral solution, 8 mg, 16 mg, and 24 mg extended-release oral capsules, and 4 mg, 8 mg, and 12 mg oral tablets[55]. Common side effects like nausea, vomiting, diarrhea, dizziness, headache, and loss of appetite. Fever, racing heart, enlarged lymph nodes, cheeks, lips, tongue, rash, pale red pimple, and breathing issues are some serious health effects that patient might face while undertaking Galantamine[56]. Since Galantamine is anti-apoptotic therefore its antioxidant property makes it neuroprotective[57],[58], [59], [60].

4.3. Rivastigmine

Rivastigmine as shown in Figure 6 (3) is also considered one of the drugs to treat dementia caused due to Alzheimer's disease. This drug is intended to treat mild to severe AD; the FDA approved it in 1997[61]. It acts as a pseudo-irreversible inhibitor of butyrylcholinesterase (BuChE) and AChE. AChE is mostly found at the synaptic neuron junction and in the high-activity area of the cerebral cortex. However, BuChE, which helps to mediate cholinergic activity, is present in brain glial cells[61]. In the normal brain, BuChE exhibits just 10% of AChE activity, but in the brain of an Alzheimer's patient, this activity can reach 40–90%. As a result, the ACh activity is decreased concurrently, which indicates that the BuChE action implies mild to severe AD[29]. Rivastigmine is usually available as liquids and pills that are taken orally. This pills are administered orally in the range of 6 to 12mg while the transdermal patches are applied topically in the dosage of 13.3mg[61]. Anorexia, asthenia, dyspepsia, nausea, vomiting, confusion, muscular cramps, weakness, and weight loss are common side effects[3], [29], [61].In the recent study, it was shown that Rivastigmine has gastrointestinal side effects[62].

4.4. Memantine

Memantine as shown in Figure 6 (4) inhibits the glutamate receptor subtype known as N-Methyl-D-aspartate receptor (NMDAR). Over activation of NMDAR results into neuronal loss or degeneration which worsens both acute and long term neurological condition such as dementia[63]. The main function of memantine is to reduce the neurotoxicity in AD[64]. Because of their low affinity they are generally used in conjunction with acetylcholinesterase inhibitors to treat AD[29], [63]. They are used to treat moderate and severe forms of dementia and are often administered through oral routes in form of liquids, tablets and capsules. During clinical studies the most frequent effects observed were constipations, dizziness, headaches, confusions and diarrhea[65].Fatigue, soreness, elevated blood pressure, hallucination, stomach discomfort, increased weight, disorientation, disruptive behaviour, and involuntary urination are additional side effects[66].

4.5. Aducanumab

Another medication used to treat Alzheimer disease is Aducanumab. It was approved by US FDA on June 2021[67]. Aducanumab is marketed as Aduhelm and are used in treat mild cognitive impairment or mild dementia stage of the disease[68]. Aduhelm was approved under accelerated approval pathway which provides an early access to drugs for patients with serious disease[69]. The removal of amyloid beta is done by the help of this monoclonal antibody. The clearance of amyloid beta is completely done by presenting it towards the microglia for phagocytosis[70]. Aducanumab are available in single dose vials for intravenous infusion treatment. A minimum of 21 days is required between IV infusions, which should be given every 4 weeks. The recommended duration for administering the infusion is one hour[71]. Apart from its benefits this drug also shows some adverse side effects in which the most common effect is amyloid related imagining abnormalities (ARIA)[67], [72]. This is commonly represented as temporary swelling in the areas of the brain and does not cause symptoms but some people might face headache, confusion, dizziness or nausea. An additional concern with Aduhelm is the possibility of hypersensitivity responses, such as urticaria and angioedema[67].

4.6. Lecanemab

Leqembi is another name for the monoclonal antibody drug Lecanemab[73]. This immunotherapy drug works by targeting β-amyloid to stop the formation of amyloid plaque[74], [75]. They are also called as antibody intravenous (IV) infusion treatment as the IV is given every two weeks and lasts for about an hour[76]. The FDA expedited Lecanemab approval for treatment of AD on January 6, 2023. And on July 3 2023, it was finally given an approval as a drug to treat Alzheimer by FDA[77]. Allergic response to Lecanemab can be severe. Headaches, infusion related side effects, and

amyloid-related imaging abnormalities (ARIA) were the most frequent side effects. Generally, ARIA is asymptomatic but tiny areas of bleeding inside or on the surface of the brain may be observed sometimes a typical brief swelling might occur which goes away over time[78]. Other symptoms like headache, disorientation, dizziness, altered vision, nausea, and seizures can also be experienced. Leqembi is also associated with a risk of infusion-related responses, which can manifest as changes in blood pressure, nausea, vomiting, and flu-like symptoms[77].

4.7. Donanemab

Recently a new drug was approved by FDA in July 2024 called as Donanemab[47]. It is amyloid beta directed antibody which was developed by Eli Lilly and company for the treatment of Alzheimer disease[79], [80]. After Lecanemab, the medication, marketed as Kisunla, is the second to be approved by the FDA for slowing down Alzheimer's disease. Donanemab is intended to remove amyloid plaque in patients with mild dementia or cognitive impairment, exactly like Lecanemab[81]. The drug Kisunla is administered as an intravenous infusion every four weeks. Donanemab markedly reduced clinical progression at 76 weeks in individuals with early symptomatic Alzheimer disease and amyloid and tau pathology[82], [83]. Additionally, in another study the results indicated that amyloid deposits in AD might be significantly reduced by three to five intravenous doses of Donanemab 10 mg/kg[84]. There are several risk issues associated with this new medication, such as ARIA, which can cause bleeding or edema. Flu, nausea, vomiting, change in blood pressure, anaphylaxis and angioedema-like symptoms are seen due to infusion related reactions. The two most frequent adverse effects of Kisunla were headache and ARIA[82].

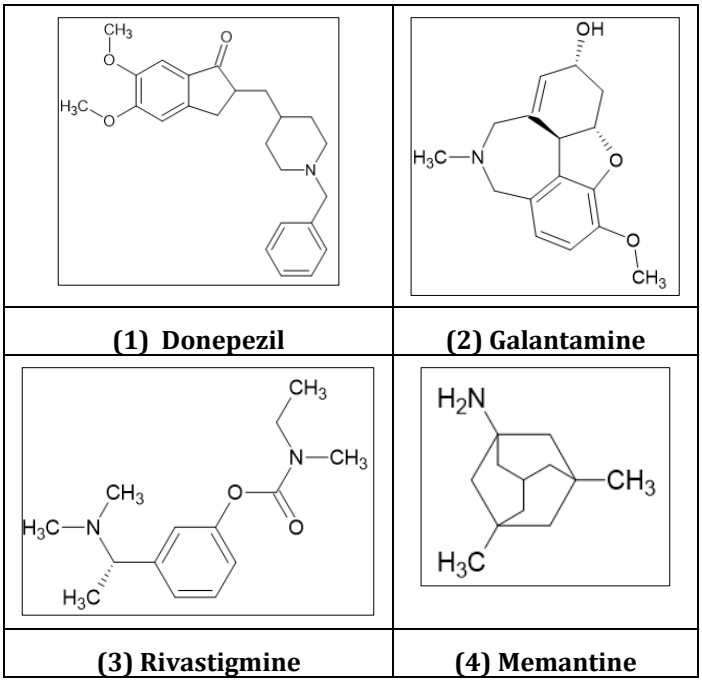

Figure 6 The chemical structure of FDA-approved drugs used in symptomatic treatments of AD

(1 Donepezil, 2 Galantamine, 3 Rivastigmine, and 4 Memantine)

According to recent research, natural products seem to lessen the signs and symptoms of Alzheimer's disease. Natural products (NP) are often used as a therapy since they are less harmful and have fewer adverse effects[85], [86], [87], [88]. Most medications made today use naturally occurring medicinal herbs in their preparation. These therapeutic herbs are widely utilized since they have minimum side effects on human health. Plant-derived natural products are essential for medication development and discovery because they are a rich source of diversely characterized bioactive compounds[89], [90]. Compared to traditional synthetic compounds, NPs have unique properties that present benefits for the drug development process. Moreover, their application in conventional treatment can shed light on their efficacy and security. Comparing the NP pool to conventional synthetic small-molecule libraries, it is generally richer in "bioactive" molecules that span a larger range of chemical space[91]. Various plant parts and marine sources include naturally occurring compounds, including flavonoids, polyphenols, alkaloids, and glycosides, which may protect against neurodegeneration and enhance cognitive and memory performance. Many natural substances have anti-Alzheimer action via certain pharmacological pathways, such as acetylcholinesterase, beta-secretase 1 , and β-amyloid targeting[92]. The Table 1 includes the natural products that have shown great efficiency towards Alzheimer's disease.

Table 1 Natural Products reported for AD

Sr. no.	Natural Products (NP)	Source Of NP	In vitro	In vivo	Clinical Trial	Biological activity	Ref
01.	Karanjin	*Pongamia pinnata*	✓	✓		Neuroprotective, antioxidant activity, and anti-inflammatory properties.	[93]
02.	*Ficus racemosa*	Bark of *Ficus racemosa*	✓			Anti-inflammatory properties enhance ACh levels, improve memory, anti-oxidant.	[94]
03.	*Punica granatum*	Pomegranate fruit				Neuroprotective, anti-inflammatory, inhibits tau protein hyperphosphorylation, BACE-1 inhibitor, and decreases amyloid deposition.	[95]
04.	*Ginkgo biloba*	Leaves of Ginkgo trees	✓	✓	✓	The anti-apoptotic effect prevents Aβ-induced neurotoxicity, neuroprotective, anti-inflammation properties, protection against mitochondria malfunction, and reduces tau protein phosphorylation.	[96]
05.	*Bacopa monnieri* (Brahmi)	Flower and leaf of *Bacopa monnieri* plant			✓	Anti-oxidant inhibits Aβ aggregation, has anti-inflammatory properties, and prevents dementia.	[97]
06.	*Withania somnifera* (Ashwagandha)	Flower, leaf, and roots of Ashwagandha	✓	✓		Improves cognitive ability, high anti-oxidant activity, inhibits the generation of amyloid plaques, minimizes destruction of brain cells, restores memory loss, and increases the level of AChE.	[98]
07.	*Nardostachys jatamansi* D.	Roots of *Nardostachys jatamansi*	✓	✓		Neuroprotective, anti-inflammatory, induces cell death of Aβ, anti-oxidant, and reduces reactive oxygen species level.	[99]
08.	*Curcuma longa*	Rhizome of curcumin	✓	✓	✓	Reduces Aβ plaques, inhibits glial cell activation, anti-neuroinflammatory, prevents cell toxicity, and improves cognitive impairment.	[100]
09.	*Zingiber officinale*	Rhizome of *Zingiber officinale*	✓	✓	✓	High anti-oxidant and anti-inflammatory properties induce cell death and anti-aggregation of Aβ.	[101]
10.	*Moringa oleifera*	Leaf of *Moringa oleifera* plant				Decreases oxidative stress, shows memory-enhancing effects, neuroprotective, and anti-cholinesterase activity.	[102]
11.	*Melissa officinalis*	Leaf of *Melissa officinalis* plant	✓	✓		Cholinesterase inhibitor, anti-oxidant, and neuroprotective.	[103]
12.	Rosmarinic Acid	Leaf of *Rosmarinus officinalis*			✓	It inhibits β amyloid formation, reduces cholinesterase in the brain, and enhances the cognitive effect and memory.	[104]

13.	Seaweed	Marine algae	✓			Anti-tumour activity, anti-oxidant activity, anti-neuroinflammatory agent, cholinesterase inhibitory activity, and inhibition of neuronal death.	[105]
14.	*Salvia miltiorrhiza* B.	Roots of *Salvia miltiorrhiza* B.	✓	✓	✓	Neuroprotective potential, anti-apoptotic, anti-amyloid-β, antioxidant, acetylcholinesterase inhibitory, and anti-inflammatory properties.	[106]
15.	*Panax ginseng*	Roots of *Panax ginseng*	✓	✓		Enhanced memory retention decreases brain Aβ production, prevents cognitive dysfunction, and accumulation of amyloid plaque, and is anti-inflammatory.	[107]
16.	*Sida rhombifolia*	Dried leaf and root of the *Sida rhombifolia*	✓			Anti-inflammatory, acetylcholinesterase inhibition, Aβ- degradation, and neuroprotective.	[108]
17.	*Convolvulus pluricaulis*	All the parts of the herb, *Convolvulus pluricaulis*	✓	✓		Neuroprotective, anti-oxidant, immunomodulatory, anti-convulsant, and Alzheimer's disease-reversing effects.	[109]
18.	*Pistacia lentiscus*	Essential oil of Pistacia lentiscus				Antioxidant, anti-inflammatory, neuroprotective, and hepatoprotective effects.	[110]
19.	*Salvia officinalis*	Leaves of *Salvia officinalis*	✓			Anti-inflammatory, anti-oxidant, memory improving activity, inhibit AChE.	[111]
20.	*Viscum album* L.	Leaves of *Viscum album* L.	✓	✓		Neuroprotective, shows BDNF-stimulating capacity against $AlCl_3$, inhibition of amyloid β protein, induces neurotoxicity, and low inhibition of cholinesterase.	[112]
21.	*Tinospora cordifolia*	Stem of *Tinospora cordifolia*	✓	✓		AChE and BuChE inhibitory activity	[113]
22.	*Uncaria tomentosa*	Specific Peruvian source	✓	✓		Prevents the formation / aggregation of plaques and tangles	[114]
23.	*Hibiscus sabdariffa* L.	Anthocyanin-rich extracts of *Hibiscus sabdariffa* L.	✓			Prevents memory impairment, anti-inflammatory, anti-acetylcholinesterase, antioxidant, anti-amyloid genic activities and induces neuroinflammation.	[115]
24.	*Lepidium meyenii*	Roots of *Lepidium meyenii*	✓	✓		Improves memory impairment, antioxidant and AChE inhibitory activities.	[116]
25.	*Pistacia atlantica*	Leaves and flowers	✓			Good antioxidant activity and inhibits the activity of acetyl- and butyrylcholinesterase	[117]

Considering the fact that the age group affected by Alzheimer's disease has undergone a sharp increase, there has also been a sudden surge in the requirement for anti-AD medication preparation. To study each natural product and its activity for a particular disease is not feasible. As a result, utilizing *in silico* techniques such as molecular docking analysis, molecular dynamic simulation, and ADMET for virtual screening of natural products in the search for effective new medications lowers the risk, expense, and duration of drug discovery[118]. Screening of ligands based on their pharmacokinetic characteristics minimizes the odds of failure during clinical trials. Computational chemistry is therefore an excellent tool for evaluating and using natural products for efficacy.

5. *In Silico* study of Natural products through Molecular Docking

In silico approaches have gained popularity as a means of circumventing the limits of in vitro and in vivo investigations, which have been utilized for a long time. Generally speaking, the term "*in silico*" refers to "on a computer or via computer simulation"[119]. Utilizing techniques like databases, data mining, homology models, machine learning, pharmacophores, quantitative structure-activity connections, and network analysis tools, these computational methods are utilized to investigate the pharmacological hypothesis. Furthermore, a variety of pharmacological qualities, including protein-ligand interactions, their capacity for absorption, distribution, and physiological mechanism, as well as discovery, optimization, and other attributes including toxicity, are discovered via the use of *in silico* approaches[120]. Two main approaches are used *in silico* drug design are Structure based drug design (SBDD) and Ligand based drug design (LBDD). The distinction between the two approaches is based on the targeted protein's availability. When the targeted proteins are unavailable, the LBDD approach is employed; in contrast, the SBDD method uses known protein structures. The most popular three-dimensional approach for finding novel drugs is called SBDD[121]. Molecular docking, molecular dynamic simulation, and ADMET analysis are typically included[122].

Molecular docking is a crucial computational technique used to predict the binding affinity of the ligand with the protein molecules[123]. This approach aimed to predict the stability and structure of the ligand-receptor complex that results from the interaction between the ligand and protein[124]. When the drug molecules reach the biological system, this interaction can immediately indicate the kinds of cellular reactions that might be occurring[124]. The binding affinity and additional details about the specific receptor location where ligand binding is occurring are released by the molecular docking program[125]. Molecular docking is also utilized in targeted protein docking. The discussion below will address the utilization of natural products in molecular docking, including their binding affinity and the optimal binding energy for estimating novel drug development. Karanjin, *Bacopa monnieri*, Rosemary diterpenes, *Malus domestica*, and *Tinospora cordifolia* are the natural compounds and derivatives in discussion.

5.1. Software Specifications

The Molegro Virtual Docker Program (MOE), AutoDock Vina, docking server (Mcule), and AutoDock tools like PyRx 0.8 software are the programs used for molecular docking. To visualize the two- and three-dimensional interactions between ligand and receptor proteins, PyMol and Discovery Studio are used.

5.2. Preparation of Receptor and Ligands

The crystalline structures of receptor proteins may be found using the Protein Data Bank. The PDB IDs for the natural products under discussion are TACE (PDB ID: 2OI0), GSK-3 (PDB ID: 1Q5K), ACE (PBD ID: 1O86), and BACE1 (PBD ID: 4DJU) for Karanjin. As for *Bacopa Monnieri* it is AChE (PDB: 3ZLT). About the diterpenes in rosemary, AChE (PDB: 1C2B). AChE (PDB:7E3H) and BuChE (PDB:7AIY) for *Malus domestica*. In contrast, AChE (PDB: 4PQE) and BuChE (PDB: 6ESY) for *Tinospora cordifolia*. In the meanwhile, the PubChem database is used to extract the ligand structure.

5.3. Molecular Docking

The docking score, according to the AutoDock program, is always expressed as a negative number; a larger negative number denotes a higher potency[126]. The natural product Karanjin was docked with four AD-related proteins. The binding energy score of Karanjin with different proteins are shown in Table 2[93]. In which it showed a higher binding score with TACE (PDB ID: 2OI0) and the lowest with ACE (PBD ID: 1O86). While the standard drugs show a binding score in the range of −5 to −11 kcal/mol. This score range depicts that the Karanjin has a similar potency as the standard drug and can be used as lead component in the treatment of AD.

Table 2 Binding Energy score of Karanjin**[93]**

Karanjin/ Standards	**ACE (PBD ID: 1O86) (kcal/mol)**	**BACE1 (PBD ID: 4DJU) (kcal/mol)**	**GSK-3 (PDB ID: 1Q5K) (kcal/mol)**	**TACE (PDB ID: 2OI0) (kcal/mol)**
Karanjin	-7.54	-8.79	-8.23	-9.40
Donepezil	- 8.88	-9.21	-7.69	-11.00
Galantamine	-7.42	-7.06	-6.68	-8.20
Rivastigmine	-6.47	-6.66	-5.31	-7.30

Twelve phytocompounds from *Bacopa monnieri* were docked with the protein AChE (PDB: 3ZLT). Of these, bacopaside X, apigenin, quercetin, wogonin and oroxindin exhibited the lowest binding energies as per the Table 3, indicating a high binding score and greater efficacy with the receptor[127]. Those phytocompounds have binding energies of −17.87, −16.71, −16.53, 15.56, and −15.05 Å kcal/mol. In which, bacopaside X, apigenin and quercetin showed the highest binding energy out of all, therefore turning into a promising anti-AD drug.

Table 3 Binding Energy score of *Bacopa monnieri***[127]**

Phytochemicals of B. monnieri	**AChE (PDB ID: 3ZLT) (kcal/mol)**
Apigenin	−16.71
Luteolin	−13.45
Quercetin	−16.53
Bacosterol	−10.45
Brahmic Acid	-13.52
Oroxindin	-15.05
Stigmasterol	-11.48
Wogonin	-15.56
Bacoside A	-12.47
Bacoside B	-12.47
Bacoside I	-11.37
Bacopaside X	-17.87
Donepezil (Reference Drug)	-8.16

Likewise, for Rosemary diterpenes, the Rosemanol (R=CH3) with a binding score of -7.270 kcal/mol revealed the lowest binding energy when docked with AChE (PDB: 1C2B) as per the Table 4[128]. Thus, indicating that there is a favourable binding between this rosemary extract and the AChE. These results suggest that rosemary diterpenes have medicinal potential for the treatment of Alzheimer's.

Table 4 Binding Energy score of Rosemary diterpenes**[128]**

Rosemary diterpenes	**AChE (PDB: 1C2B) (kcal/mol)**
Carnosic acid	−5.560
Carnosol	−6.142
Rosmanol (R = H)	−6.383
Rosmanol (R = CH3)	−7.270
Epirosmanol	−7.130
Isorosmanol	−6.464
12-Methoxyl carnosic acid	−5.735
11,12-Dimethoxy isorosmanol	−6.071

Similarly, *Tinospora cordifolia* isolated compound Tinosporide and 8-hydroxytinosporide when docked with AChE (PDB: 4PQE) according to the Table 5 they showed the docking score of -8.7 kcal/mol and -9.9 kcal/mol which is relatively more as compared to the Donepezil whose score is -8.3 kcal/mol[113]. When this isolated compound when docked with BuChE (PDB: 6ESY) also showed relatively high scores. Among these, 8-hydroxytinosporide demonstrated a nearly identical binding score to Donepezil, proving its efficacy in treating AD.

Table 5 Binding Energy score of *Tinospora cordifolia***[113]**

Tinospora cordifolia	**AChE (PBD ID: 4PQE) (kcal/mol)**	**BuChE (PBD ID: 6ESY) (kcal/mol)**
Donepezil (std)	−8.3	−9.9
Tinosporide	−8.7	−8.8
8-hydroxytinosporide	−9.0	−9.5

Lastly, the two natural components of *Malus domestica* (apple) were docked with two proteins, AChE (PDB:7E3H) and BuChE (PDB:7AIY). The docking score of these proteins are listed in Table 6 and are compared to the commonly used medication Rivastigmine[129]. Compared to the standard, which has a docking score of -7.8 kcal/mol, the compound with CIDs: 107905 and 12000657 had a high score in the range of -11 to -12 kcal/mol. When this compound with CIDs: 107905 and 12000657 was docked with BuChE, the range was greater (-10.0 to -11.2 kcal/mol) than it was with the standard. Thereby, making it the most effective lead component for Alzheimer disease treatment.

Table 6 Binding Energy score of *Malus domestica***[129]**

Compounds	**AChE (PDBID: E3H) (kcal/mol)**	**Compounds**	**BuChE (PDB:7AIY) (kcal/mol)**
Rivastigmine (std)	-7.8	Rivastigmine (std)	−6.8
(-)-Epicatechin gallate CID: 107905	-12.2	[(2R,3S,4S,5S,6S)-6-[5-[(2S)-5,7-dihydroxy-4-oxo-2,3-dihydrochromen-2-yl]-2-hydroxyphenoxy]-3,4,5-trihydroxyoxan-2-yl] methyl (E)-3-(4-hydroxyphenyl) prop-2-enoate CID: 163103561	−11.2

4-((4′-(Aminomethyl)-[1,1′-biphenyl]-3-yl) oxy) pyrimidine-2-carbonitrile CID: 12000657	-11.6	Folic acid CID: 135398658	−10.0

With the aid of the discovery studio, which provides additional details on the bonds that are present, the visualization of the three-dimensional interaction between the receptor and ligand can be examined. For instance, several bond types, such as van der waals bonds, conventional hydrogen bonds, carbon-hydrogen bonds, alkyl, pi-alkyl, and pi-sigma bonds, are seen in the natural product. This software makes all of this information available. Furthermore, it identifies the specific ligand location that is bound to each kind of protein amino acid. This can be well illustrated by an example of *Malus domestica*. Figure 7 represents the molecular docking of AChE protein with a standard Rivastigmine, Epicatechin gallate of CID: 107905 and 4-((4′-(Aminomethyl)-[1,1′-biphenyl]-3-yl)oxy)pyrimidine-2-carbonitrile of CID: 12000657[129]. The compounds with CID: 107905 and CID: 12000657 interacted with protein AChE and resulted into the formation of total of six hydrogen bonds each, and their amino acid residues were involved not only in Van der Waals interactions but also in Pi–Pi interactions which, with the help of Discovery Studio, can easily be understood.

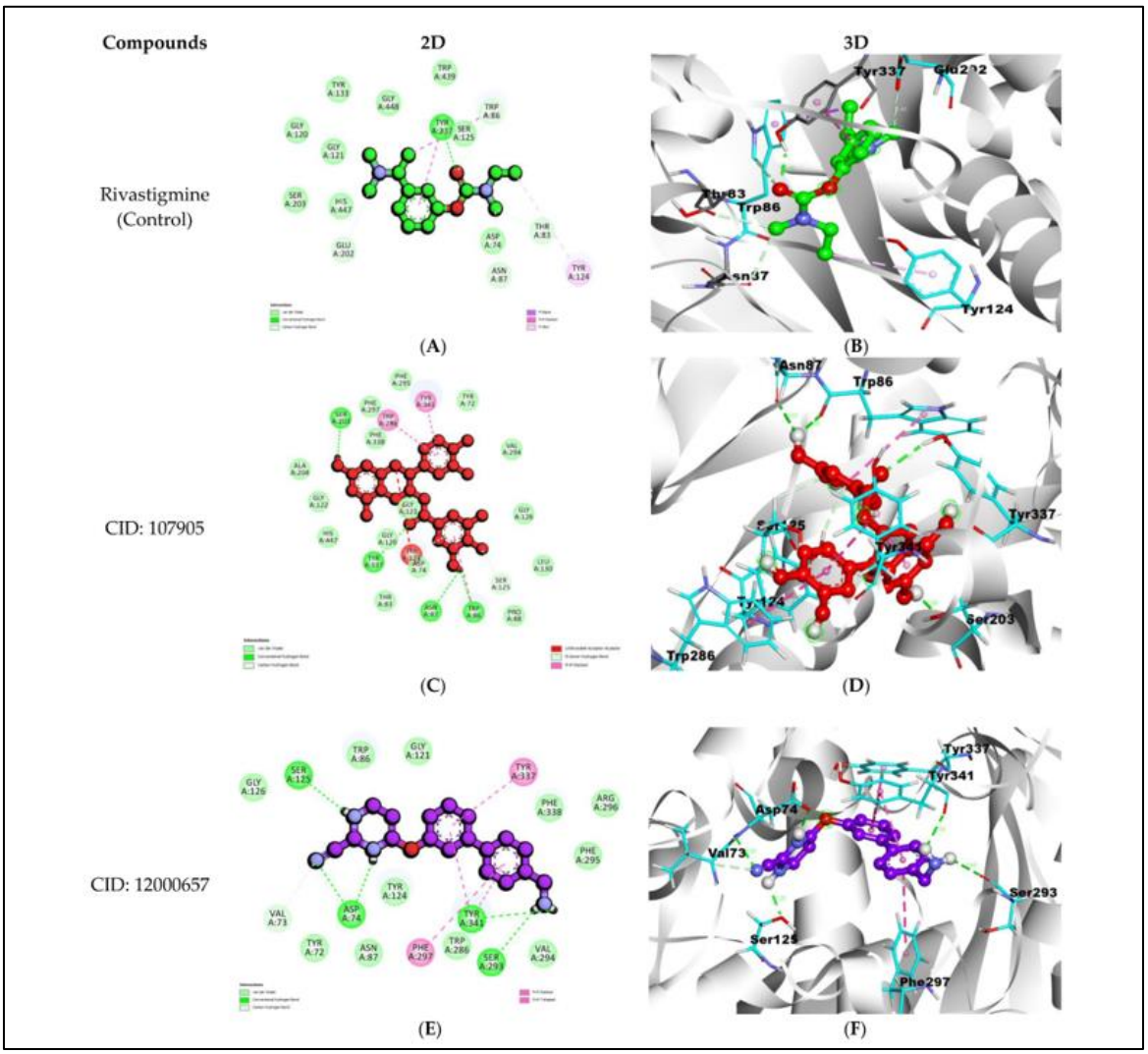

Figure 7 Molecular docking of AChE with natural compounds of apple. Adapted with the permission of ref **[129]**

In the same way, when BuChE interacted with compounds of CID: 163103561 and CID: 135398658 resulted into seven hydrogen bonds. The amino acid residues of these compounds showed the presence of Van der Waals interactions and Pi–Pi T-shaped bonds. However, other interactions were also observed such as hydrogen bonding, hydrophobic interactions, and Pi–Pi interactions. The Figure 8 illustrates the docking analysis and visual representation of receptor

BuChE with two ligands[129]. One identified as CID number 163103561 and the other, as folic acid, with CID number 135398658.

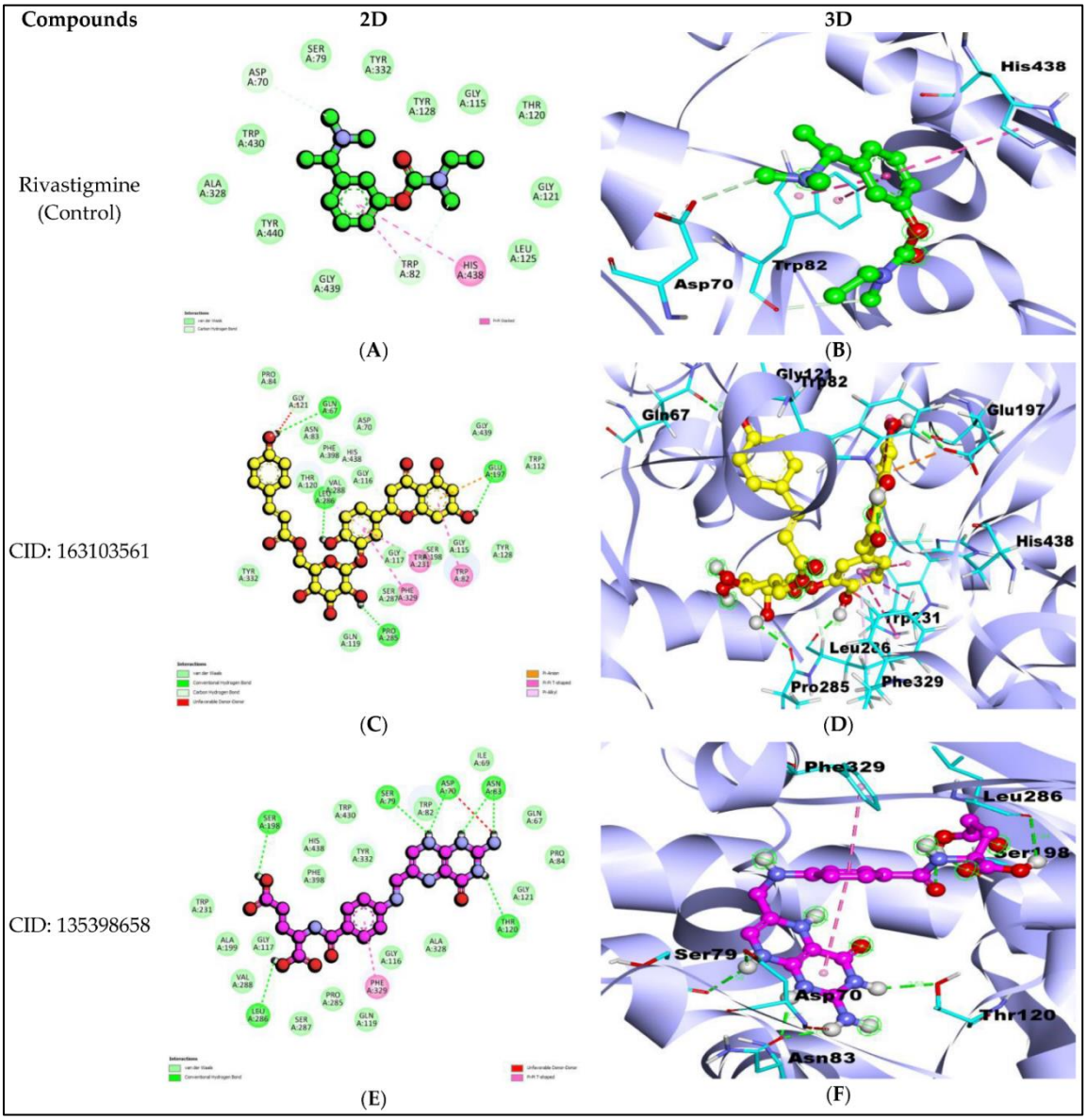

Figure 8 Molecular docking of BuChE with natural compounds of apple. Adapted with the permission of ref **[129]**

6. Molecular Dynamic Simulation

In modern drug development, molecular dynamic simulation has recently shown great development. An approach to study the physical behaviour of atoms and molecules in a system is referred as Computational Molecular Dynamic (MD) Simulation[130]. This method was employed to overcome a significant restriction on complex calculations. Because it was computationally difficult, molecular dynamics simulations overcame this difficulty by simulating atomic movements using straightforward calculations based on Newton's equations of motion[124]. Using mathematical algorithms, molecular dynamic simulation can determine how atoms and molecules will move over time given their initial locations, velocities, and external influences[130]. Because of this, scientists can see how different circumstances affect the interactions between drugs, proteins, and other molecules as well as their surroundings.

6.1. Software Specifications

GROMACS 2022, a NAMD program, is capable of doing molecular dynamic simulation. On the other hand, CHARMM provides the ligand topology. The Visual Molecular Dynamic (VMD) 1.9.3 program may be used to determine RMSD values.

6.2. Molecular Dynamic Simulation of Natural Product

RMSD, or root mean square deviation, and RMSF, or root mean square fluctuation, are two crucial quantities in molecular dynamics (MD). The RMSD measure aids in highlighting structural alterations and stability in MD. Significant conformational changes during simulation are reflected in higher deviations or variations seen in RMSD plots, which are suggestive of molecular instability[131]. RMSF analysis is essential for computing residue variations during simulation as its value can change the energy of ligand binding interaction. A smaller RMSF value denotes a strong secondary structure, whereas a greater value suggests flexible parts in the structure[132]. The RMSD plot of the protein-ligand complex for *Catunaregam spinosa* was determined at a 50 ns trajectory. As per the Table 7, the complexes 1GQR (orange), 1QTI (yellow), and 4PQE (green) had the lowest RMSD values of 0.202 nm, 0.227 nm, and 0.395 nm, respectively[132]. The three other ligands that displayed the highest RMSD values observed were 0.244 of 1QTI - butanoic acid, 3-methyl-2- [(phenyl methoxy) imino]-, trime, 0.245 was seen in 1GQR - 1,4,7,10,13,16-hexaoxacyclooctadecane, and 0.296 nm was of 4PQE - butanoic acid, 3-methyl-2- [(phenyl methoxy) imino]-, trime. Furthermore, RMSF values were performed for 1GQR, IQTI and 4PQE. The standard showed RMSF values of 0.135, 0.140, and 0.190 nm while the ligand showed RMSF values of 0.133, 0.146, and 0.159 nm. These results imply that the RMSF values can vary depending on the presence of specific receptor and ligand used during the process. The presence of minimum fluctuation indicates its effectiveness as a potential drug. *Bacopa monnieri* is another natural product that was assessed using MD modelling; in this case, the RMSD value was obtained at a 50 ns trajectory. The protein-ligand complexes of AChE-quercetin and AChE-apigenin had a value range of 0.45 to 1.9 Å according to the Table 7[127]. However, a little variation in AChE-apigenin was noted as well as fluctuations were also observed in AChE-quercetin. At RMSF peaks, protein fluctuation is most frequently seen. Peak maxima for apigenin, quercetin, and bacopaside X were observed at 2.7, 2.9, and 4 correspondingly. These values represent tolerable RMSF variations, indicating the formation of a stable combination. Thus, making *Bacopa monnieri* a strong candidate for anti-Alzheimer drug. The simulation in Novel Compounds as per Table 7 took 35ns to complete[124]. Galantamine had a greater fluctuation in the RMSD plot than the other, however, this is still acceptable because it remained steady over time. In the RMSF plot, Galantamine had more disturbance and fluctuation at residue 100, while Zoladex displayed fluctuation at residue 360. Conversely, the two remaining complexes, CHEMBL-1240685, and Donepezil, had fluctuations within the range of 0.1nm to 0.25nm and appeared to exhibit less flexibility. High RMSF value indicates that protein-ligand interactions are not maximum and the binding efficiency is low. Among all four, CHEMBL-1240685 displayed the lowest RMSD value, indicating a higher level of receptor affinity as well as great binding affinity of ligand. Therefore, we can infer that CHEMBL-1240685 is a potential hit molecule that can be used effectively in Alzheimer treatment. Lamiaceae family, the RMSD plot was seen after the simulation ran for 200ns. GSK-3β and its complex with ATP, Apigenin, Luteolin, Rosmarinic acid, and Salvianolic acid had values of 0.228, 0.227, 0.229, 0.226, 0.219, and 0.220 as shown in Table 7[131]. The system exhibited high stability in the RMSF plot, with the exception of one residue, which showed reduced volatility and mobility. Thereby, Lamiaceae family is another effective natural product for treating AD.

Table 7 Molecular Dynamic Simulation values of reported Natural Products

Natural Products	Complexes	RMSD	RMSF	Ref
Catunaregam spinosa	1GQR - 1,4,7,10,13,16-hexaoxacyclooctadecane	0.245 ± 0.038 nm	0.146 ± 0.068 nm	[132]
	1GQR - tacrine	0.202 ± 0.019 nm	0.135 ± 0.068 nm	
	1QTI - butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-, trime	0.244 ± 0.027 nm	0.133 ± 0.081 nm	
	1QTI - tacrine	0.227 ± 0.030 nm	0.140 ± 0.079 nm	
	4PQE - butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-, trime	0.296 ± 0.043 nm	0.159 ± 0.078 nm	

	4PQE - tacrine	0.395 ± 0.049 nm	0.190 ± 0.080 nm	
Bacopa monnieri	AChE-apigenin	0.45-1.9 Å	2.7 Å	[127]
	AChE-quercetin	0.45-1.9 Å	2.9 Å	
	AChE-bacopaside-X	0.45-3.0 Å	4 Å	
Novel compounds	Donepezil	0.1-0.2 nm	0.1-0.25 nm	[124]
	Galantamine	≥ 0.2 nm	HIGH (at 100 residues)	
	Zoladex	0.1-0.2 nm	HIGH (at 360 residues)	
	CHEMBL-1240685	0.1-0.2 nm	0.1-0.25 nm	
Lamiaceae Family	GSK -3β in apo(enzyme)	0.228 nm	0.05-0.45 nm	[131]
	Adenosine triphosphate	0.227 nm		
	Apigenin	0.229 nm		
	Luteolin	0.226 nm		
	Rosmarinic acid	0.219 nm		
	Salvianolic acid	0.220 nm		

Figure 9 shows the RMSD plot of molecular dynamic simulation analysis of one of the natural product that is *Catunaregam spinosa*[132]. Here, the RMSD plot was run for 50ns trajectory. The RMSD values for the standard 1GQR-tacrine complex of orange colour was the lowest at 0.202 nm, followed by 1QTI-tacrine represented by yellow at 0.227 nm and 4PQE-tacrine green in colour was at 0.395 nm. Similarly, ligands showed the highest RMSD values which were 0.244 of 1QTI-butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-, trime represented by gray, 0.245nm of 1GQR-1,4,7,10,13,16-hexaoxacyclooctadecane was displayed as blue, and 0.296 nm of 4PQE-butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-, trime was represented by green colour respectively.

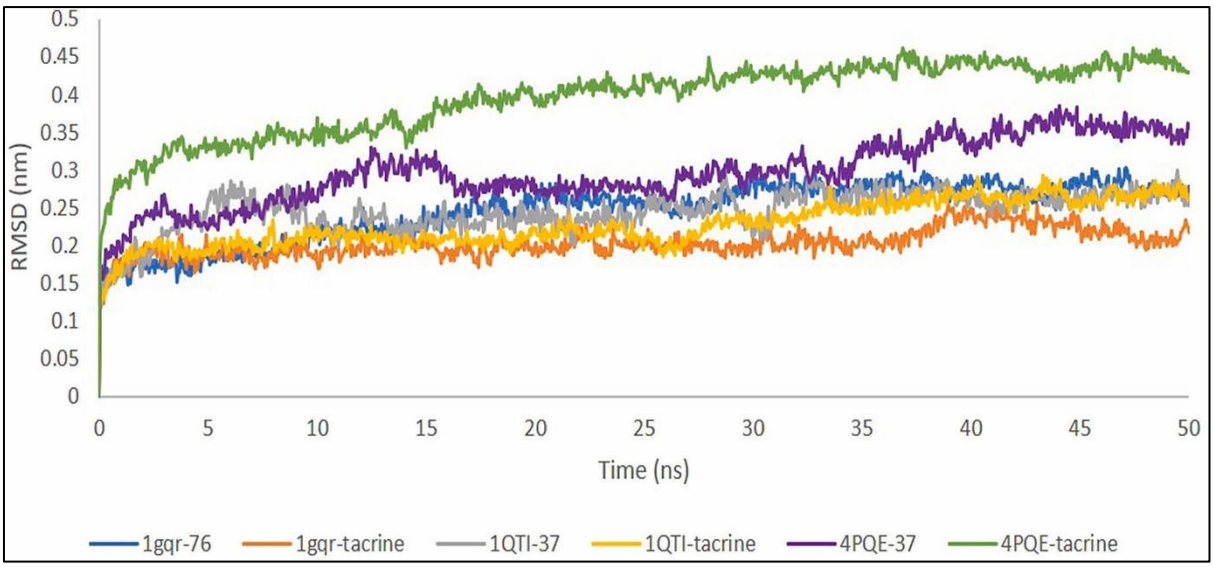

Figure 9 RMSD plot of *Catunaregam spinosa* reprinted with permission from ref [132] copyright © 2024 The Authors. Published by Elsevier Ltd

Additionally, the Figure 10 represents the Root Mean Square Fluctuation (RMSF) of ligands and its standard[132]. The RMSF values 0.135, 0.140, and 0.190 nm of 1GQR, 1QTI and 4PQE tacrine standard complex were observed. However, the 1QTI (butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-, trime showed the RMSF value at 0.133nm, while 1GQR (1,4,7,10,13,16-hexaoxacyclooctadecane) was observed at 0.146nm and 4PQE (butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-, trime) ligand complex had RMSF values of 0.159 nm respectively. From RMSF graph, we can determine where residue peak formation occurs. The residue peak of 1GQR – 1,4,7,10,13,16-hexaoxacyclooctadecane was observed at 534, 107, likewise 1GQR – tacrine residues were observed at 534, 535. Similarly 1QTI complex with butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-,trime residues were at 534, 284, while its complex with tacrine the peak was observed in flexible region at 534, 535,similarly 4PQE-butanoic acid, 3-methyl-2-[(phenylmethoxy)imino]-,trime residues were seen at 495, 496 and lastly 4PQE-tacrine showed residue at 506, 166, are all analysed on the basis of RMSF values. From this analysis we can calculate the residue fluctuation during simulation. Moreover, the high RMSF value suggests structure's flexible region whereas low RMSF value represents that complex contains a good secondary structure. It also helps us comprehend the interaction between proteins and ligands. The pharmacodynamics and pharmacokinetics of the drug compounds were well-informed by the molecular dynamic simulation[124].

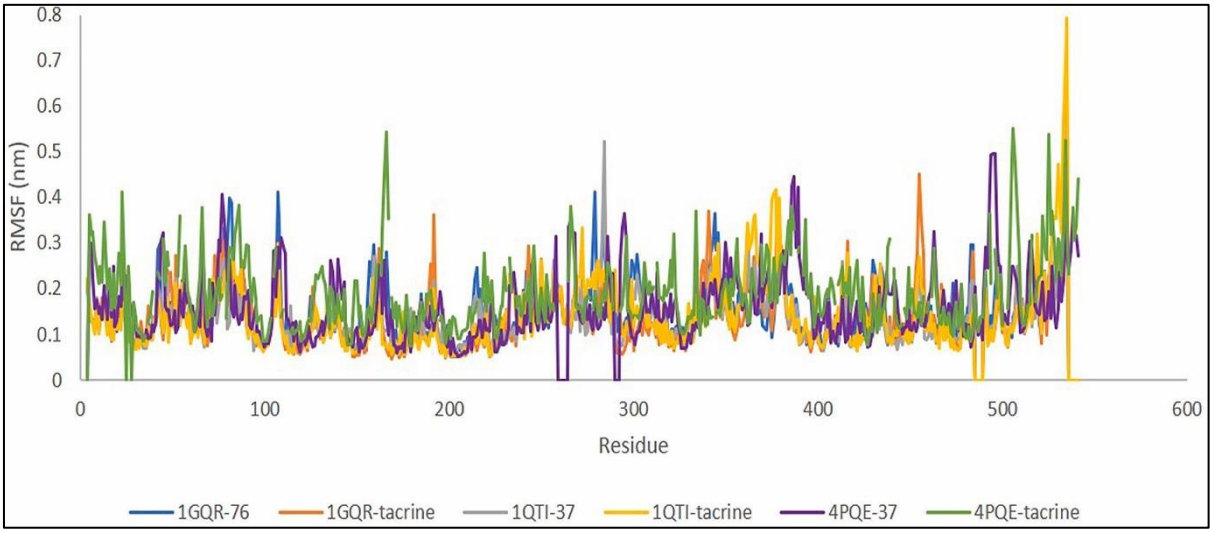

Figure 10 RMSF plot of *Catunaregam spinosa* reprinted with permission from ref **[132]** copyright © 2024 The Authors. Published by Elsevier Ltd

7. ADMET Study

ADMET stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity[133]. ADMET study provides substance's pharmacokinetic profile which is important for assessing before they are put into the market as medicinal molecule[134]. It reveals the degree to which the drug supports our metabolic system or the degree of absorption in the gastrointestinal system. Additionally, it alerts us about the potential for nephrotoxicity and neurotoxicity from the medication being metabolized[135]. This is examined by using software like SwissADME. The ADME properties of candidate compounds includes additional parameters such as the Lipinski rule of five and molecular refractivity, TPSA value, MLogP (Moriguchi octanol-water partition coefficient), GI absorption, and BBB permeant (which indicates whether or not the drug is passing the blood-brain barrier)[136], [137]. The bioavailability score is also included, which indicates whether or not the medication can be taken orally. Through ADME study, one may understand about pain warnings and synthetic capabilities. Acute oral toxicity, carcinogenetic characteristics, and ADME toxicity were also computed using the SwissADME and admetSAR servers. The chemicals that were extracted from *Tinospora cordifolia*, Tinosporide and 8-hydroxytinosporide, demonstrated favorable findings in terms of their physicochemical characteristics, lipophilicity, water solubility, pharmacokinetics, and drug-likeness (Lipinski rule of five), without any form of violation as shown in Table 8[113]. Based on the ADMET features, all of the medications have respectable pharmacokinetic profiles and both ligands meet Lipinski five rules. And according to the result, the best option for treating cognitive impairment would be the ligand 8-hydroxytinosporide, whose outcomes are quite similar to Donepezil. Thus, these compounds may offer the best qualities of drugs and might be effective treatments for AD.

Table 8 ADMET study of *Tinospora cordifolia***[113]**

→ NATURAL PRODUCTS	**Donepezil**	**Tinospora cordifolia**	
↓ ADMET PARAMETERS		**Tinosporide**	**8-hydroxytinosporide**
Molecular Refractivity	115.31	198.19	166.61
TPSA	38.77	32.23	35.5
MLOGP	3.06	3.32	2.97
GI absorption	High	High	High
BBB permeant	Yes	Yes	Yes
Lipinski #violations	0	0	0
Ghose #violations	0	1	0
Veber #violations	0	0	1
Bioavailability Score	0.55	0.30	0.27
PAINS #alerts	0	0	0
Leadlikeness #violations	2	3	1
Synthetic Accessibility	3.62	2.55	3.38
Ames Mutagenesis	Negative	Negative	Negative
Acute oral toxicity	III	III	III
Eye Irritation	Negative	Negative	Negative
hERG	Positive	Negative	Negative

Abbreviations

- AD: Alzheimer disease.
- NMDA: N-Methyl-D-aspartate.
- EOAD: Early onset Alzheimer disease.
- LOAD: Late onset Alzheimer disease.
- PSEN1: Presenilin 1.
- PSEN2: Presenilin 2.
- APP: Amyloid precursor protein.
- ROS: Reactive oxygen species.
- NMDAR: N-Methyl-D-aspartate receptor.
- CNS: Central nervous system.
- Aβ: Amyloid beta.
- GSK-3β: Glycogen synthase kinase 3-beta.
- PP2A: Protein phosphate 2A.
- FDA: Food & Drug Administration.
- AChE: Acetylcholinesterase.
- BuChE: Butyrylcholinesterase.
- AChEI: Acetylcholinesterase inhibitor.
- ACh: Acetylcholine.
- ARIA: Amyloid related imagining abnormalities.
- NP: Natural Product.
- ADMET: Absorption, Distribution, Metabolism, Excretion, Toxicity.

- SBDD: Structure Based Drug Design.
- LBDD: Ligand Based Drug Design.
- MD: Molecular Dynamic.
- RMSD: Root meant square deviation.
- RMSF: Root means square fluctuation.

8. Future prospective

Alzheimer's Disease is considered the fifth deathliest disease and has a significant impact on the health, economy, and societies of the world. A wide range of pharmaceuticals have been introduced and are constantly being developed to provide anti-AD treatments. Many ongoing research has proven that natural products are considered an important source of novel, potent drugs for treating neurodegenerative illness due to their anti-inflammatory, antioxidant, and neuroprotective properties. According to the data mentioned in the review, natural products have proved to be promising in treating Alzheimer's disease. Rather than using traditional methods like in vivo, and in vitro individually, we can compile them together along with the advances of *in silico* studies, then this conventional approach will prove to be more deserving and productive. Utilizing computational techniques will make natural products more cost-effective and efficient. With the use of the *in-silico* technique, we may even utilize a variety of natural product derivatives to determine their effectiveness. Molecular simulation and structure-based drug design can be used to discover treatments for AD. Their effectiveness as therapeutic molecules were demonstrated by drug-likeness, ADMET analysis, and molecular dynamic simulations (RMSD and RMSF). Despite the recent advances and focus weighing more on computational methods and *in silico* techniques there is still more scope in a new generation of drug discovery which includes Multi-target drugs, Novel trial designs, Blood-based biomarkers, use of Artificial Intelligence (AI), and Machine Learning which is a potentially useful approach for detecting individuals at risk of AD. As seen in Figure 11, this demonstrates how the future approach outweighs the current approach.

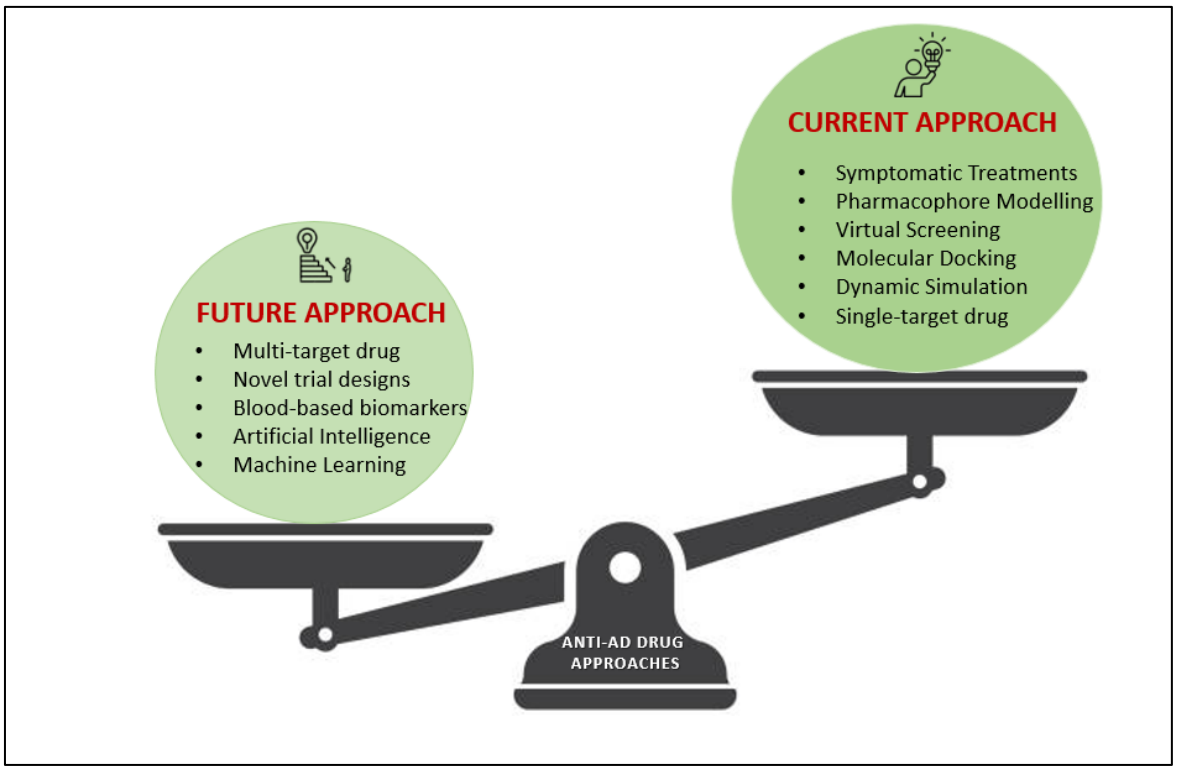

Figure 11 Approaches for treating Alzheimer Disease

9. Conclusion

It has also been indicated by current research that the cerebral cortex can access tiny drugs for AD using nanocarriers. Developing phytochemicals (antioxidant and anti-inflammatory polyphenols) should be given first priority. As a result, the conclusion drawn from our reviews is that combining natural products with *in silico* techniques would inevitably

lead to a better knowledge of the receptor, ligands, and eventually Alzheimer's disease itself. It is also shown that natural products are ultimately the best suitable preliminary candidates to alleviate the burden of Alzheimer's disease patients, families, and the public health system by contributing to the discovery of novel drugs against Alzheimer's disease.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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