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BY

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I, Murali Mohan Mishra, a 2K21/IBT/13 student of M. Tech. INDUSTRAL BIOTECHNOLOGY, hereby declare that the dissertation project I submitted to the Department of Biotechnology at Delhi Technological University, Delhi, in partial fulfilment of the requirement for the award of the degree, is titled "Finding common involution between Type 2 Diabetes and Alzheimer's Disease (Type 3 diabetes) and the recent advancement in their therapeutic regime using computational approach." This work is original and does not contain any undocumented copying from other sources. In completing this assignment, I have adhered to the standards of academic integrity and have upheld all the student code of conduct.

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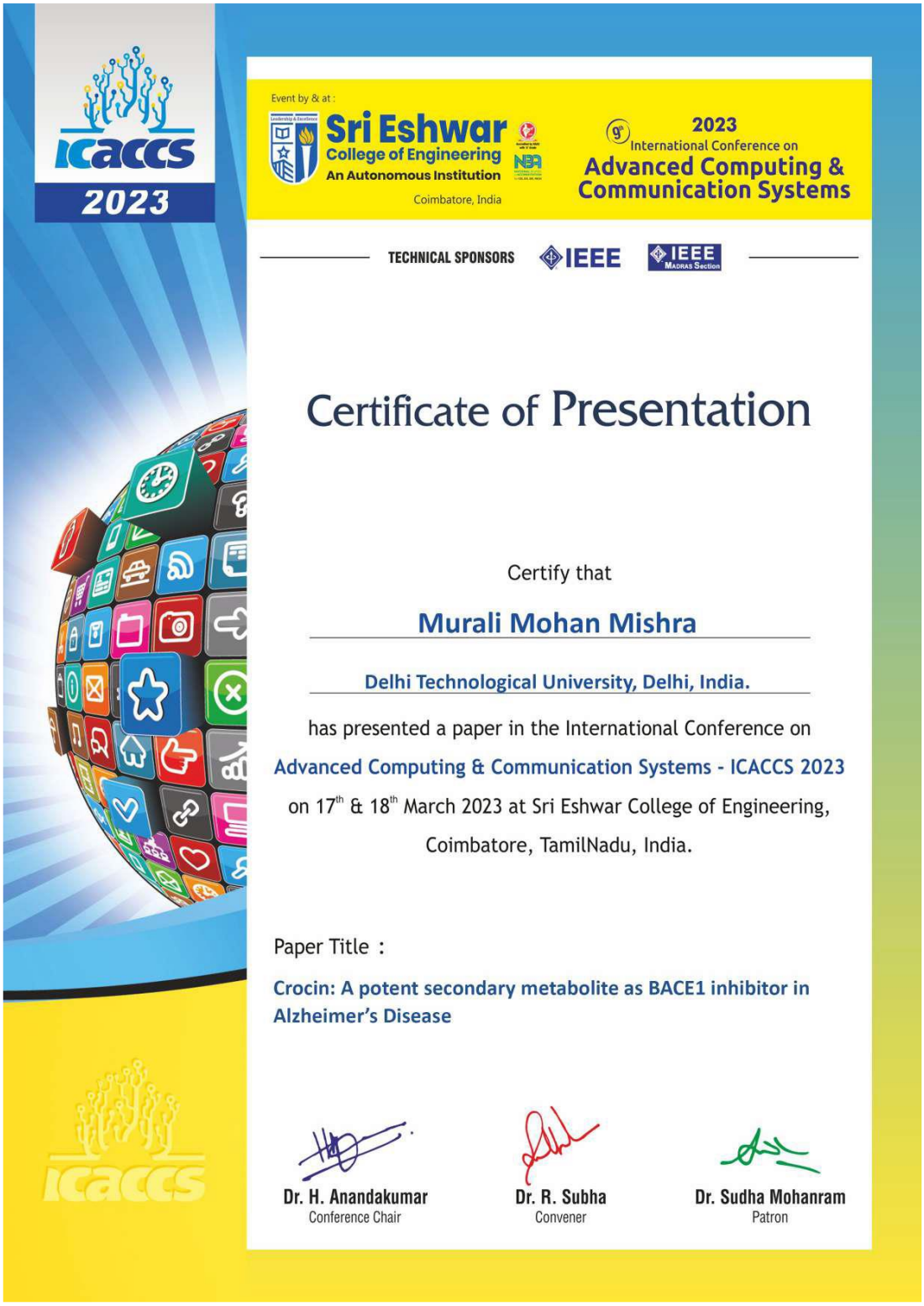
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This is to certify that the dissertation project being submitted by Mr. Murali Mohan Mishra, 2K21/IBT/13, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology, is a record of his work on finding common involution between Type 2 Diabetes and Alzheimer's Disease (Type 3 diabetes) and the recent advancement in their therapeutic regime using computational approach. As far as I'm aware, this work hasn't been submitted in full or in part for a degree or diploma at this university or anywhere else.

31/05/2023

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ABSTRACT

More than 44 million people worldwide suffer with Alzheimer's disease (AD), a neurodegenerative condition which shows amyloid peptide accumulation, development of neuro-fibrillary tangles, and tau proteins hyperphosphorylation. Several variables, including insulin resistance, hyperglycaemia, protein misfolding, and altered equilibrium between amyloid peptide integration and disintegration, are to blame for the beginning of AD and the course of the disease. The effectiveness and serious complexity of the therapeutic techniques now utilised to treat disease have a variety of constraints. Therefore, the need for a superior therapeutic agent that can meet the demand for AD treatment is crucial in the current environment. The current project focuses on therapeutic approaches that are both now in use and being developed to treat AD and other neurodegenerative diseases. To paint a clear picture of the important therapeutic candidates for the AD treatment, the study addressed in detail all the available plant-based secondary metabolites and FDA-approved medication candidates.

In this project we have used computational approach for the study of various pharmacokinetic properties of potential therapeutic agents wherein we have performed molecular docking of various therapeutic candidates with respective target molecules to evaluate their binding energy. Further, we have performed thorough analysis of these therapeutic agents for their suitable pharmacokinetic characteristics using SWISS ADME online server tool. At last, we have discussed about the development of combinatorial and synergistic drug formulation and multi-target-domain-ligand (MTDL) drug formulation that are the recent developments in the therapeutic strategy .

Keyword- **Alzheimer’s disease; amyloid β; neurodegenerative disease; Type 3 diabetes; neuroendocrine; Synergistic and combinatorial drug; multi-target-ligand-domain (MTDL), molecular docking, SWISS ADME.**

1. INTRODUCTION

The prevalent form of dementia is Alzheimer's Disease (AD), a neurological progressive illness that starts with memory loss[1]. It entails the degeneration of brain regions responsible for memory, thinking, and language processing. More than 6.7 million people will be diagnosed with the illness in 2023 alone.[2].] According to estimates, the population with AD with age more than 65 is speculated to get double every 5 years, with symptoms initially appearing after age 60 and risk rising with age [2]. The major causes for AD are- aggregation of beta amyloid peptide in CNS that forms senile plaques, hyperphosphorylation of Tau peptide forming neuro fibrillary tangles, decline in various neurotransmitter such as Acetylcholine, norepinephrine, and serotonin, disturbed equilibrium between synthesis and clearance of amyloid beta peptide, dystrophic neurites, blockage of energy metabolism, chronic oxidative stress, mitochondrial dysfunctioning, damage of DNA and halted expression of pro-apoptotic genes and their signalling mechanism[1,3–6]. AD is characterized by some of the pathological conditions such as- cognitive dysfunction of the nervous system, neuroinflammation, protein misfolding and death of neuronal cells [7,8].

The preceding outcome is determined to be a connection between decreased blood glucose metabolism and AD. Recently, it was shown that the primary component causing the onset and progression of AD is insulin resistance or insulin-like growth factor.[9,10]. They have role in modulating the metabolism of nervous system and the nerve cell growth and differentiation. Any obstruction among these factors may results in the lost control of the signalling mechanism of the nervous system and eventually leads to apoptosis of the neuronal cells[11–13]. Some recent studies suggest that metabolic disorders arising due to insulin dysfunctioning is linked to resulting dementia in type 2 diabetes[14]. Further, few common characteristics between type 2 diabetes and AD has been established such as increased cholesterol level, insulin resistance in CNS and PNS, damaged signalling cascade of IR, ageing related disorders and the degeneration of neuronal cells. It was found that hyperinsulinemia may fasten the progression of AD as compared to normal conditions. In addition, a connection between an atypical cascade of IR signalling and the decreased expression of genes that code for insulin in AD patients was discovered, leading to the classification of AD as a neuroendocrine

disease[15–17]. AD is now called as type-3 diabetes because it shares many characteristics with the type-1 and type-2 diabetes. Even after such a huge increase in the population suffering from AD, the therapeutic modalities currently available for AD's treatment is very restricted. The available therapeutics have lots of side effects which find an important reason for the research and development work to be carried forward on a high pace for the discovery of efficient drug and other treatment modalities for the AD and other life-threatening neurodegenerative disease. In this project we have worked upon the role of various available drugs for the AD's treatment and have studied the recent advancement in the therapeutic modalities of the neurodegenerative disease including AD.

2. LITERATURE REVIEW

2.1 Neurodegenerative disease

The progressive loss of the structure or functionality of neurons, or neurodegeneration, is the root cause of neurodegenerative diseases. Cell death may ultimately result from such neural injury. Amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple system atrophy, and prion disorders are a few examples of neurodegenerative illnesses[18]. From the molecular to the systemic levels of neural circuitry, neurodegeneration can be seen in the brain. These illnesses are regarded as incurable because there is no known mechanism to stop the ongoing destruction of neurons; nonetheless, research has revealed that inflammation and oxidative stress are the two main contributors to neurodegeneration[19,20]. Atypical protein assembly (like proteinopathy) and triggered cell death are two examples of the many commonalities between these disorders that have been found in biomedical research at the subcellular level[21]. These parallels imply that therapeutic developments for one neurodegenerative illness may also benefit other diseases. In terms of neurodegenerative disorders, it is predicted that 139 million individuals would have dementia globally by 2050, up from the expected 55 million in 2019[22].

2.2 Alzheimer's disease

Alzheimer's Diseases (AD) is a neurobiological progressive disease that begins with loss of memory and is considered to be the most common type of dementia[23]. It involves degradation of the parts of brain that controls memory, thoughts, and the

language processing functionality. In the year 2023 alone more than 6.7 million people are found to have diagnosed with the disease. Beyond the age of 65, the population living with the AD is speculated to get doubled after every five years wherein the symptoms appear firstly after the age of 60 with the progression of risk with increasing age. The finding of scientist tells us that there are multiple factors that can influence the person differently such as age, family history and lifestyle. The major causes for AD are- aggregation of beta amyloid peptide in CNS that forms senile plaques, hyperphosphorylation of Tau peptide forming neuro fibrillary tangles, decline in various neurotransmitter such as Acetylcholine, norepinephrine, and serotonin, disturbed equilibrium between synthesis and clearance of amyloid beta peptide, dystrophic neurites, blocked energy metabolism, chronic oxidative stress, mitochondrial dysfunctioning, DNA damage and halted expression of pro-apoptotic genes and their signalling mechanism. AD is characterized by some of the pathological conditions such as- death of neuronal cells, cognitive dysfunction of the nervous system, neuroinflammation, protein misfolding.

2.3 AD as Type 3 Diabetes

Decreased blood glucose metabolism is found to be associated with AD as the preceding consequence. Recently it has been found that insulin resistance or insulin-like growth factor are the key factor responsible for the development and progression of AD. They have important role in regulating the metabolism of nervous system and the nerve cell growth and differentiation. Any obstruction among these factors may results in the lost control of the signalling mechanism of the nervous system and eventually leads to apoptosis of the neuronal cells. Some recent studies suggest that metabolic disorders arising due to insulin dysfunctioning is linked to resulting dementia in type 2 diabetes. Further, few common characteristics between type 2 diabetes and AD has been established such as increased cholesterol level, insulin resistance in CNS and PNS, damaged signalling cascade of IR, ageing related disorders and the degeneration of neuronal cells. It was found that hyperinsulinemia may fasten the progression of AD as compared to normal conditions. Additionally, a link between unusual cascade of IR signalling and the decreased expression of genes code insulin was found in the patients of AD due to which AD has now been considered as a neuroendocrine disease. Due to various similarities with type 1 and 2 diabetes, AD is now considered as type 3 diabetes.

2.4 Amyloid β and Tau Pathology

In the patients suffering from AD, a synergistic relationship has been found between amyloid β accumulation and the Tau hyperphosphorylation [9]. In an in-vitro study conducted in mice model of AD, it was found that due to multiple factors were associated with cause of disease and thus there was not much difference between the stage of impairment and cognition when only the senile plaques were removed from AD mice[9]. On the other side it was reported that if the production of amyloid β was stopped it ultimately resulted in the reduced pathology of the Tau peptides and the subsequent increased production of amyloid β resulted in the increased Tau pathology[24]. In a study carried out in the organoid brain culture of stem cells (IPSCs) from the AD patients, antibodies against amyloid β reduced the development of AD in the early phases[12]. Further, a correlation between total Tau and the phosphorylated tau was seen only when under the condition where amyloid β aggregation was substantial[25].

2.5 Insulin-resistance and GSK3β

Insulin-resistance is related with the disturbed GSK3β in direct or indirect ways. Pathological conditions involving insulin resistance often leads to hyperinsulinemia. Signal dysfunctioning of insulin and IGF-1 leads to Tyr 216 phosphorylation resulting in the enhanced activity of GSK3β which eventually increases the level of blood glucose [26]. In a study where Wnt pathway was blocked, inhibition of GSk3β was observed which led to the increased blood glucose level[27]. On the other side it was also reported that hyperphosphorylation of GSK3β results in decreased islet β proliferation eventually resulting in hyperinsulinemia[28]. This observation proved that any sort of disturbance in GSK3 β pathway leads to insulin resistance and thus results in the increased blood glucose level.

2.6 Insulin resistance and MAPK pathways

Directly or indirectly, MAPK (Mitogen activating protein kinase) regulates insulin resistance significantly. It is made up of 14 components and is divided into four major sub-categories including- ERK 1, ERK5, JNK 1/2 and p38[29]. When the ERK1 is up taken it gets phosphorylated it recruits Grb2 peptides with Src homology 2-domain and forms a complex with GEF which activates Ras-GTP leading to the phosphorylation of Raf. Ras-GTP complex is then translocated to the cell membrane and further activates MAPK, serine, and threonine MAPK/ERK kinase which finally phosphorylates and actives various down streaming peptides[29–31]. As a part of direct

mechanism various pathways such mTORC1 signalling pathway, gluconeogenesis and protein synthesis are involved. On the other side indirect action includes controlling the phosphorylation of initiation regulators of protein synthesis by MNK[32,33]. ERK proteins are found to have prominent role in the phosphorylation of insulin receptors including IRS1 and IRS2. In-vitro, ERK 1 controls insulin-resistance by the action of C-June activation domain binding protein-1 (JAB1)[34]. In response to insulin, JNK is triggered in a MKK4 and MKK7 dependent manner[35–37]. As a part of direct action, it phosphorylates various nuclear targets such as perilipin and the glucocorticoid receptors in the regulation of lipolysis and indirect action is controlled through $p90^{RSK}$ activation[38,39]. Further it has been found that JNK hinders insulin resistance in a tissue dependent manner[40]. Another class of MAPK called p38 is stimulated by various oxidative stress, growth factors, inflammatory cytokines, and hypoxia[31]. As a part of direct action p38 controls FOXO, C/EBP-α and PPAR-γ while indirect action includes activation of MNK and MSK[41,42]. Further it was found that insulin resistance is regulated by p38 activation in hypothalamus[43,44]. The last MAPK sub-class called ERK5 which is known as Big Mitogen- Activated Protein Kinase1 stimulates the sensitivity of insulin in the adipocytes cells and have significant anti-inflammatory effects by the PPARS activation[45,46].

2.7 Cholinergic disturbance in AD

As a result of empirical decline, a significant decline of cholinergic neurons is seen which results in the gradual decrease in the transmission of cholinergic signals[47]. This obstruction in the cholinergic transmission process may result in the formation neurofibrillary tangles[48]. Two of the main hypotheses developed while studying AD were- "Amyloid Hypothesis" and "Cholinergic Hypothesis". The Cholinergic-Hypothesis emphasises the significance of choline functions being compromised in the neocortex and hippocampus, which are essential for memory, learning, emotions, and behavioural responses[49]. The Amyloid-Hypothesis is built on the observation that acetylcholinesterase causes secondary non-cholinergic activities, such as an increased build-up of amyloid peptides in the form of plaques or NFT in AD patients[50]. Because of the hydrolysis of acetylcholine by the acetylcholinesterase enzyme, atrophy of brain is characterised by a decrease in the number of neurotransmitters like acetylcholine, which are known for the passing of signals from one neural cell to another[51]. A prime therapeutic target for the AD"s hippocampus has been the recognizing and selection of new ACE inhibitors utilising bioinformatics methods to increase cholinergic

activity in the brain. By preventing acetylcholine and butyrylcholine from being hydrolysed, cholinesterase inhibitors improve the transmission of cholinergic impulses[52]. By hydrolysing acetylcholine, butrylcholinesterase, an enzyme closely related to acetylcholinesterase, plays a significant role in controlling cholinergic neurotransmission. According to studies, butrylcholinesterase activity rises by 40 to 90% in the brain's-hippocampus and temporal-cortex during the progression of AD[49]. The aggregation of amyloid-βpeptides at the initial stage of plaque development is mostly caused by butrylcholinesterase' s enhanced activity. By increasing the availability of acetylcholinesterase in the variously pretentious regions of the brain and reducing the deposition of amyloid-peptides, both ACE and BACE can be identified as significant targets for managing AD according to the above findings.

2.8 Secondary metabolites in AD

The search for a medicine that can stop the course of atrophy and cognitive deterioration in AD is ongoing today, but a significant lead has not yet been discovered. The pharmacological molecules that have been shown to play any therapeutic effect in AD are also quite complicated. Thus, the ability of plant-based products, particularly secondary metabolites, to stop the aggregation of amyloid peptides was investigated. Unexpectedly, it was discovered that naturally occurring plant compounds, especially secondary metabolites, played a significant effect in preventing amyloid- formation and subsequent fibrillization[53]. Due to these molecule's noncovalent attachment to the amyloid peptide, they were examined. The amino terminus of the peptide is exposed to other molecules in the A fibrils for interaction, whilst the centre and carboxyl terminal ends of the protein are linked to intra- and inter molecular binding inside the amyloid peptide[54]. The transmission electron microscopy, thioflavin T assay, scanning electron microscopy, atomic force microscopy, sandwich ELISA, and Ultra Violet spectroscopy are the techniques that are most frequently employed to examine amyloid aggregation or its fibrillization[55,56]. While its monomers do not interact with Thioflavin T, oligomers and the amyloid fibrils considerably attach to it[54,57]. According to research on the excitation spectra of Thioflavin T, amyloid incubated Thioflavin T in potassium buffer produced a stronger signal at 450 nm than Thioflavin T alone did[58]. Amyloid incubated with Thioflavin T produced an emission spectrum signal with a maximum at 480 nm, however Thioflavin alone produced no emission spectrum signal. Based on these findings, it was hypothesised that Thioflavin T attaches to the amyloid molecules' beta sheets and so offers the clearest picture

possible of how different secondary metabolites affect the aggregation and fibrillation of the amyloid peptide. Secondary metabolites having a prominent role in the prevention of amyloid β aggregation and fibrillation are discussed below.

2.8.1 Gallic Acid

The production of mature amyloid "fibrils" was shown to be avoided by a two-fold molar excess of gallic acid in the TEM analysis performed after 20 hours of fibrillization. In a different investigation, the gallic acid concentration was the same (100 M). While the TEM examination revealed that fibrils were present on the opposite side but that gallic acid had interfered with the binding of amyloid molecules in the fibrils, the thioflavin T assay demonstrated diminished fibrillization of the amyloid sheet since the fluorescence has diminished[59]. The size of the amyloid was significantly reduced after a one-month treatment with gallic acid, but not their quantity[60]. Gallic acid may be an effective multitarget pharmacological agent for managing and treating AD, according to all these data combined.

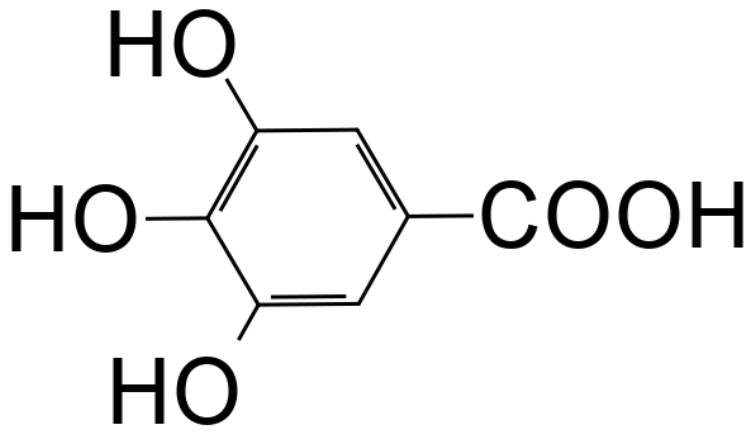


Figure 1. Gallic acid

2.8.2 Rosmarinic Acid

Amyloid peptide was treated with Rosmarinic acid at concentrations of 1, 10, 20, and 100 M for 24 hours, and this significantly decreased the amount of fluorescence that was detected using the Thioflavin T assay[61]. Additionally, a transgenic animal was given Rosmarinic acid orally for 10 months, which greatly decreased the amyloid peptides and plaques[62]. The dopaminergic synapse route, which elevated the level of monoamines in the cerebral cortex, was thought to be the fundamental mechanism causing this impact.

2.8.3 Salvianolic Acid B

It was discovered that salvianolic acid's inhibitory effect on the production of amyloid fibrils was dose dependent. With 100 M of the salvianolic acid, the greatest decrease in fluorescence was seen[63]. According to Shen et al., salvianolic acid administered intraperitoneally at dosage of 30 & 60 mg/kg for a time of 14 weeks decreased amyloid levels, hence reducing cognitive deficits[64]. This medication also improved a number of other metabolic parameters, including a decrease in plasma low-density lipoprotein cholesterol, which was positively correlated with amyloid level. These results together suggested that salvianolic acid had the ability to regulate multiple metabolites, and that its mechanism helped to reduce the amount of amyloid by inhibiting the production of the enzyme secretase, that is connected to amyloidogenic pathway, and plasma levels of low-density lipoprotein cholesterol.

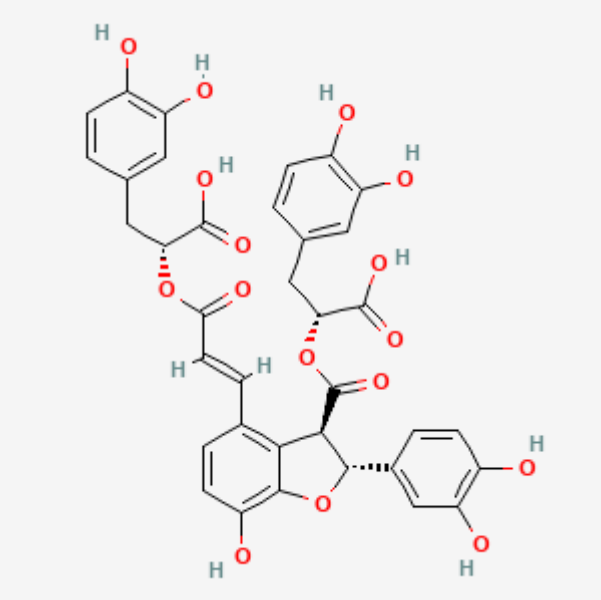


Figure 2. Salvianolic Acid B

2.8.4 Luteolin

Compared to the peptide on vehicle, amyloid- exhibited a decreased and lowered Thioflavin T test fluorescence when incubated with 100 M luteolin[65]. There was a prominent reduction in the fluorescence of the Thioflavin T assay when peptide and luteolin were incubated at a concentration of 40 M[66]. The preferred method of

administering luteolin for the treatment was intraperitoneally at a dosage of 20 mg/kg/day. The specific inhibition of GSK3 was the underlying mechanism for the decrease in amyloid aggregation.

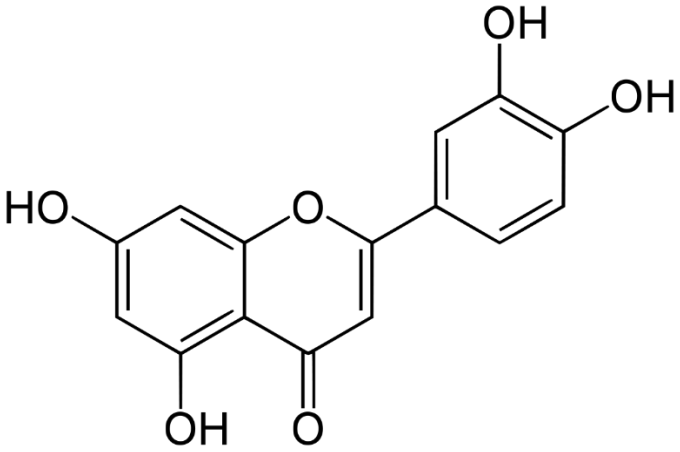


Figure 3. Luteolin

2.8.5 Quercetin

Quercetin's anti-aggregation abilities were tested at concentrations of 1, 10, and 100 M with 20 M of amyloid. When compared to the peptide on vehicle alone, the incubation mixture's fluorescence in the Thioflavin T assay was lower[65]. The triple transgenic mice received an oral quercetin gavage therapy for 12 months, with doses of 100 mg/kg given every 48 hours. This treatment had a significant impact on amyloidogenesis by reducing it[67]. It lessened the tau pathology in the hippocampus and amygdala. The amount of apolipoprotein E fragments in the cortex was increased, and the levels of amyloid were decreased, according to a study where 500mg/kg of quercetin mixed in maize oil was given orally. These effects were later identified by western blot and real-time PCR[41]. The removal of amyloid was a result of increased ApoE levels. Together, these results suggested that quercetin therapy may aid in slowing the development of AD's histopathological markers and cognitive deterioration.

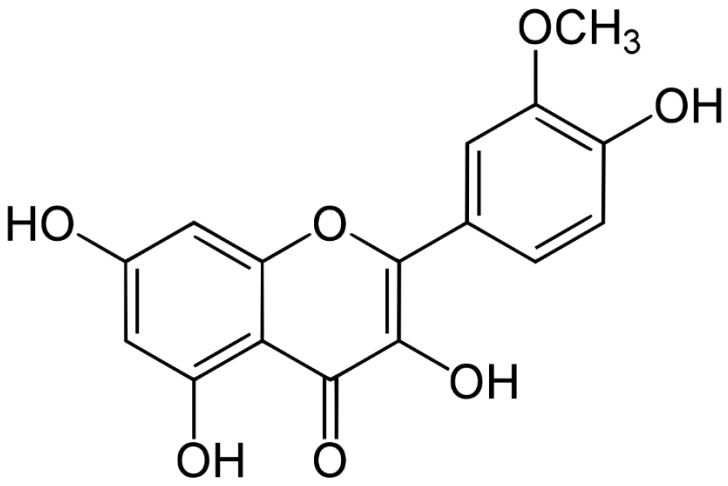


Figure 4. Quercetin

2.8.6 Fisetin

A flavanol molecule called fisetin has a variety of neuroprotective effects that have been seen in vivo, as well as neurotrophic and anti-amyloid activity in vitro[68]. By using the Thioflavin T assay, 20 M amyloid that was treated with 100 M fisetin at 370 C for 8 hours demonstrated a reduction in fluorescence to 60%[65]. Memory loss and learning impairments were shown to be prevented when fisetin was taken orally for 3 to 12 months at a dosage of 25mg/kg. Fisetin can be regarded as important therapeutic methods for AD symptoms treatment based on the findings.

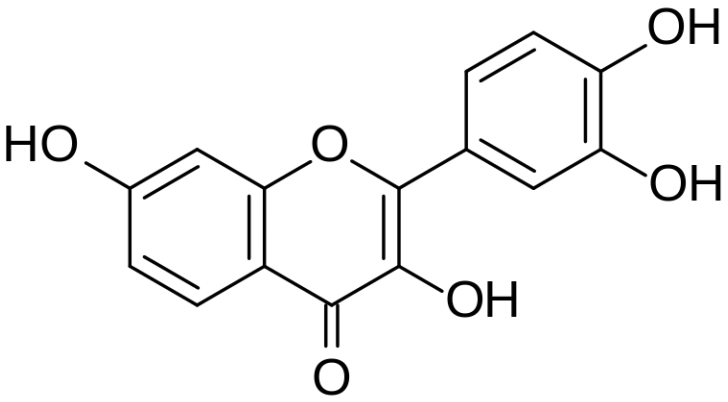


Figure 5. Luteolin

2.8.7 Myricetin

48 hours were spent incubating a solution containing 10 M of amyloid and varying concentrations of 0.1, 0.3, 1, 3, and 10 M of myricetin at 370 C. When compared to the sample alone on vehicle, it was found that the Thioflavin T assay's fluorescence was reduced to 50% at concentrations of 3 and 10 M[69]. Myricetin was given orally to

a Tg2576 female AD for 5 months, and the results showed a significant drop in A11 positive oligomers and a propensity to slow the build-up of amyloid plaque[70].

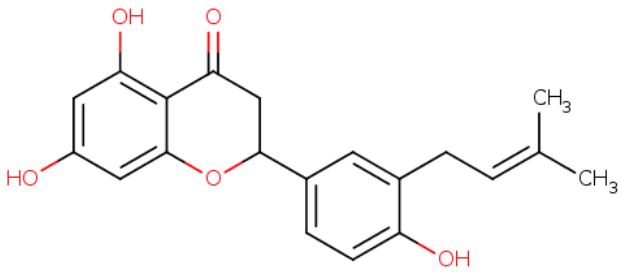


Figure 6. Myricetin

2.8.8 Dihydromyricetin

Dihydromyricetin at varying concentrations of 1, 3, 10, 30, and 90 M was treated with 30 M amyloid peptide. The thioflavin T assay results revealed that at a concentration of 90 M, the highest drop in fluorescence was seen to be 25%[70]. The restoration of gephyrin to the normal level, which is a gamma-aminobutyric acid protein (GABA) and has identified a role in regulating and plasticity of GABAergic synapse, was the fundamental mechanism behind the reduction in the aggregation of the peptide. The level of the functioning synapse and additional GABA transmission were both restored[54]. In light of these data, it was concluded that dihydromyricetin may be an important therapeutic drug for the AD treatment.

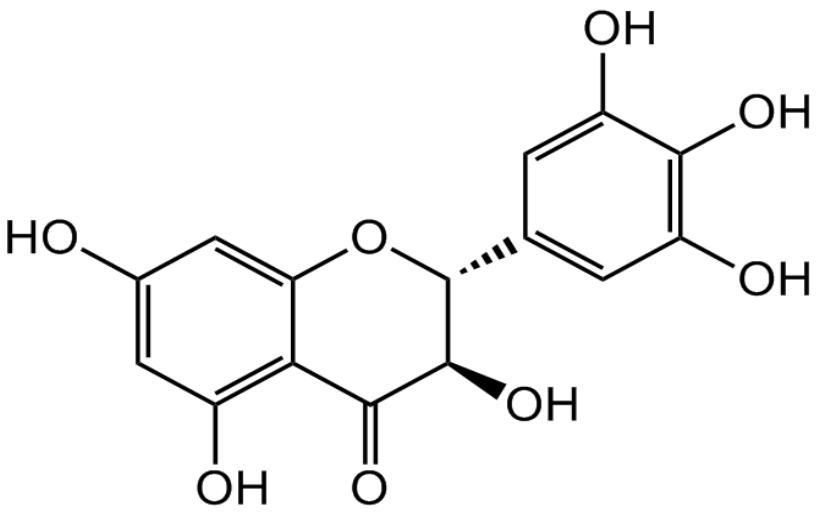


Figure 7. Dihydromyricetin

2.8.9 Silibinin

It was found that the fluorescence of the Thioflavin-T assay was reduced by 30% when amyloid at a concentration of 20 M was incubated with Silibinin at concentrations of 0.1, 1, 10, and 100 M Silibinin[71]. The cognitive deficit was improved, and the area of the amyloid plaques was reduced in the cortex and hippocampus after receiving a daily dosage of 2 mg/kg intraperitoneally for four weeks. Additionally, acetylcholinesterase activity and quantity decreased, whereas synaptic guard, neurogenesis and gliogenesis had increased[72]. Together, these findings revealed that Silibinin has a significant role in inhibiting beta-amyloid accumulation.

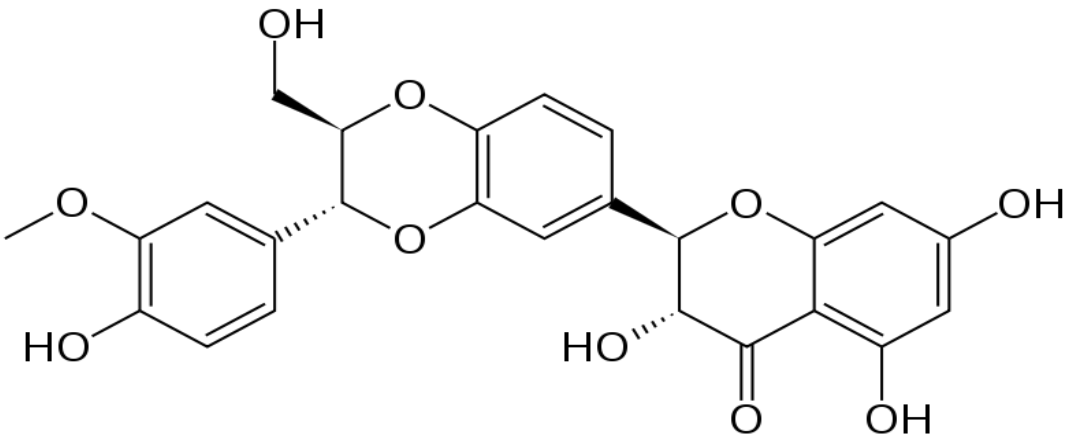


Figure 8. Silibinin

2.8.10 Oleuropein

Oleuropein and olive leaf extract both demonstrated a reduction in fluorescence for the Thioflavin-T assay of 61% and 60%, respectively, when checked for their capability to prevent the accumulation of amyloid peptides. In a study where mice received oleuropein and olive leaf extract orally for four months, it was shown that the neuropathology of the hippocampus had greatly improved, which was the cause of the amazing decrease in amyloid plaques in the mice's hippocampus and cortex[73]. The process was interference with the pace of colloidal aggregation, breakdown of the fibrils generated, and conformational preference of amyloid, which prevented further peptide aggregation[74].

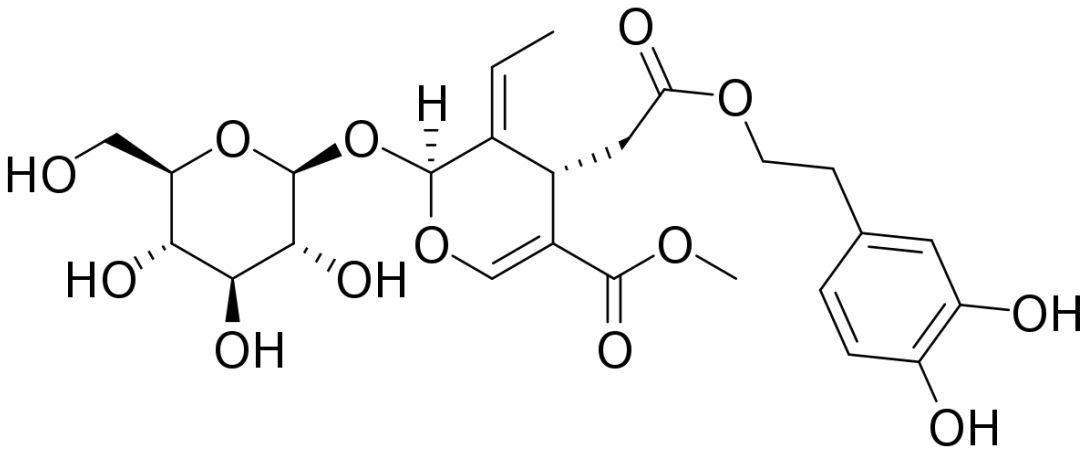


Figure 9. Oleuropein

2.8.11 Rutin

The Thioflavin T assay reading was taken every six hours while 10 M of amyloid peptide was treated with 50 and 200 M of Rutin for 24 hours. In the instance of 50 M Rutin, the results revealed a considerable drop in fluorescence, and virtually little fluorescence was seen in the case of 20 μM Rutin[75]. In a dot-blot examination using oligomer-specific antibodies that was associated with a spatial memory loss, it was shown that giving a double transgenic mouse a daily dosage of 100 mg/kg exhibited a reduction in amyloid peptide aggregation of around 60.8%[76]. Rutin therapy was also said to have reduced the frequency of astrocytosis and microgliosis & increased the function of glutathione and SOD, and considerably decreased the levels of glutathione peroxidase and malondialdehyde. Rutin-treated AD mice also showed elevated levels of the inflammatory cytokines. The mechanism underlying all these observations was the reduction of inflammatory cytokine production and suppression of glial cell activation.

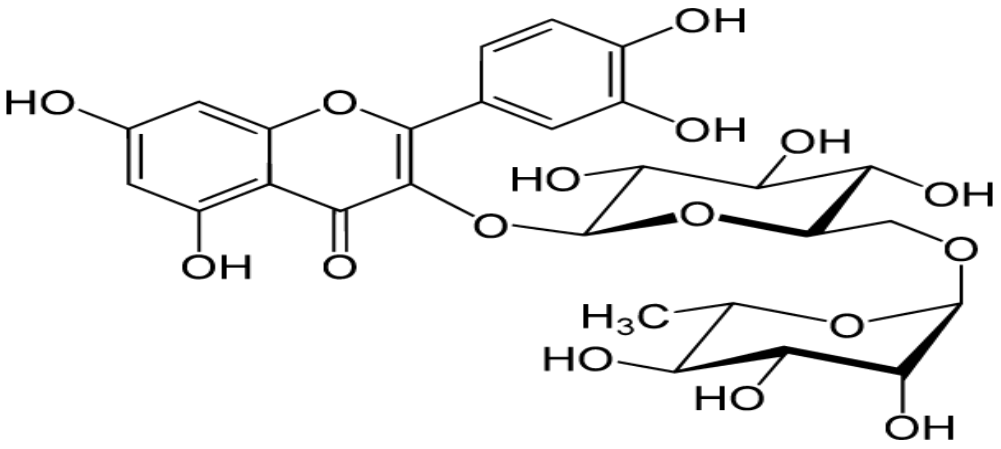


Figure 10. Rutin

2.8.12 Curcumin

It was discovered in a study that 10 M of curcumin was enough to decrease the level of fluorescence in the Thioflavin T assay[77]. A dose of 7.5 mg/kg/day of curcumin injected intravenously into the mouse's tail was said to remove and diminish the plaques by up to 30%. Additionally, it was discovered using multiphoton microscopy that curcumin may readily penetrate the blood-brain-barrier and identify plaque & brain amyloid-beta angiopathy aggregates. Additionally, it assisted in reversing structural modifications made to dystrophic dendrites. Together, these findings demonstrated that curcumin could undo the neurotoxicity brought on by pre-existing amyloid plaque deposits[78]. Compared to the control, prolonged treatment with curcumin for five months in a lower composition reduced amyloid peptide aggregation by 43%[79]. Additionally, it was noted that curcumin lowers the levels of interleukin 1 beta and oxidised protein in the treated mice's brains as well as the astrocytic marker GFAP[80]. Curcumin is discovered to have bound with amyloid at greater levels, preventing the formation of new amyloid. According to Western blot and immunohistochemical study, curcumin can decrease beta amyloid accumulation in CA1 of the hippocampus area, lower presenilin-2 expression, and increase the activity of enzymes that break down beta amyloid[55]. These results suggested that presenilin-2 inhibition or an enhanced clearance of amyloid peptides may be the fundamental mechanisms driving the anti-aggregating actions of curcumin.

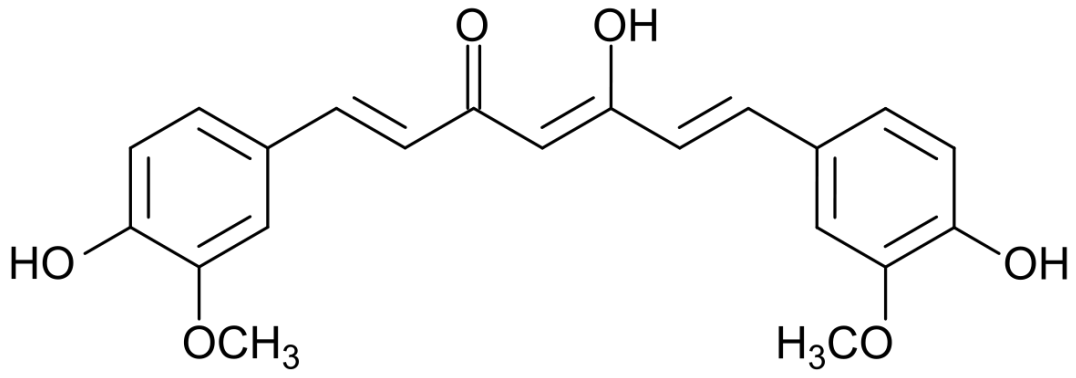


Figure11. Curcumin

2.8.13 Crocin

The aggregation of peptides was seen to have decreased to 63 to 66% approximately when the amyloid peptides were treated with 15.4 mM of crocin for 2 to 3 hours at 37^0C[57,81]. Additionally, it was administered as a dietary supplement for a month, and the results revealed a 29% decrease in amyloid aggregates[82]. The increased utterances

of Neprilysin (NEP) and the elevated ApoE clearance mechanism were thought to be the causes of this decrease in aggregation.

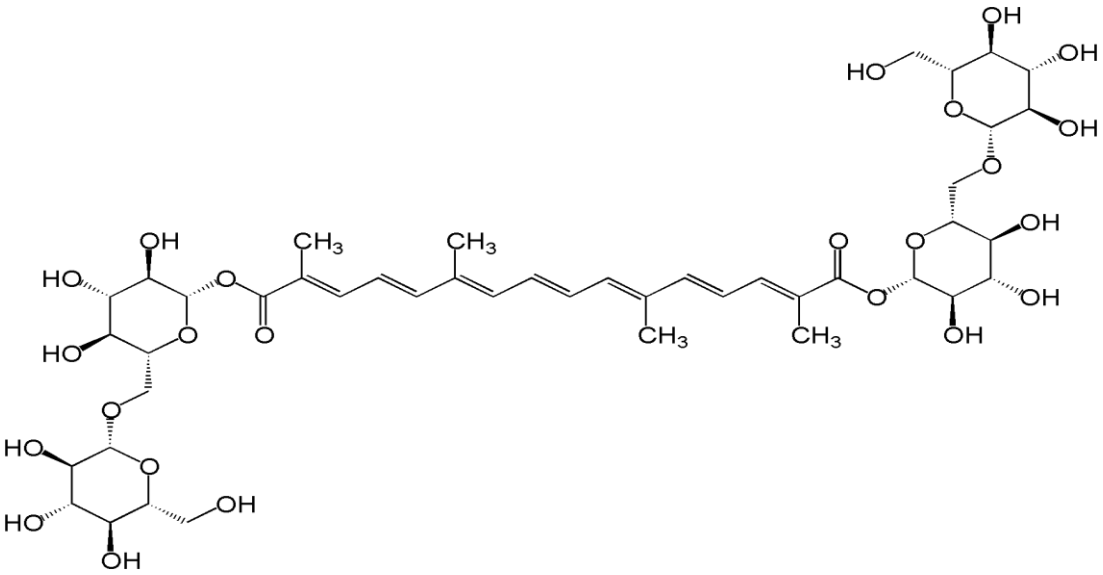


Figure 12. Crocin

2.8.14 Cryptotanshinone

At 37^0C for 37 hours, 10 M of the amyloid peptide was incubated with varying concentrations of cryptotanshinone (1, 2.5, and 5 M). Thioflavin T test fluorescence was observed to have dropped to 44% in the instance of a 5 M concentration 107. The intensity of fluorescence rapidly decreased when cryptotanshinone concentration was raised. Further, a deficit in spatial learning and memory was corrected after a long course of therapy using Morris water maize at dosages of 5, 15, and 30 mg/kg/day. The increase of -secretase is the underlying mechanism for this beneficial effect of cryptotanshinone on amyloid.

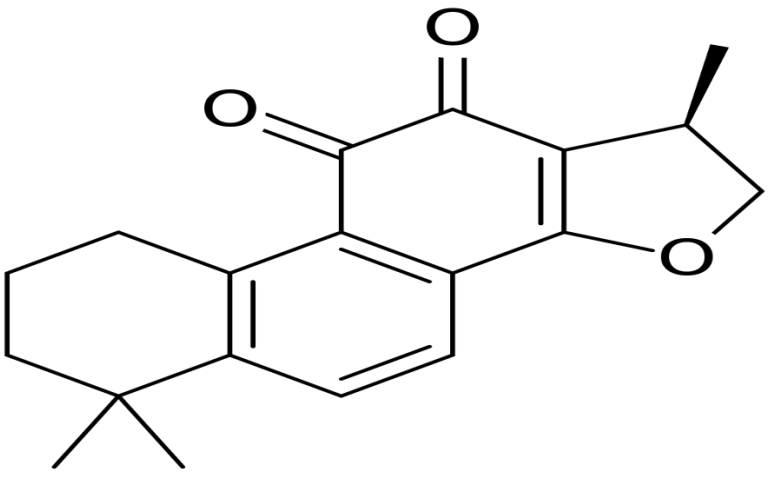


Figure 13. Cryptotanshinone

2.8.15 Epigallocatechin-3-gallate

The resultant fluorescence in the Thioflavin T assay was decreased to a very low value when amyloid protein was kept with 40 M of epigallocatechin-3-gallate (EGCG) (a peptide sequence KLVFF reflecting the sequence of amyloid peptide was complexed with EGCG)[83]. 20mg/kg/day of ECGC intraperitoneally administered for two months significantly decreased the amyloid level in the cerebral cortex[84]. Additionally, an immunohistochemistry assay showed that the hippocampus area and the cortical region of the brain both had an amyloid plaque reduction of 47–54% and 38%, respectively. Memory impairment and corrected spatial learning are both effects of EGCG. All these findings suggested that systemic administration of epigallocatechin-3-gallate can reduce brain insulin resistance in AD animal models.

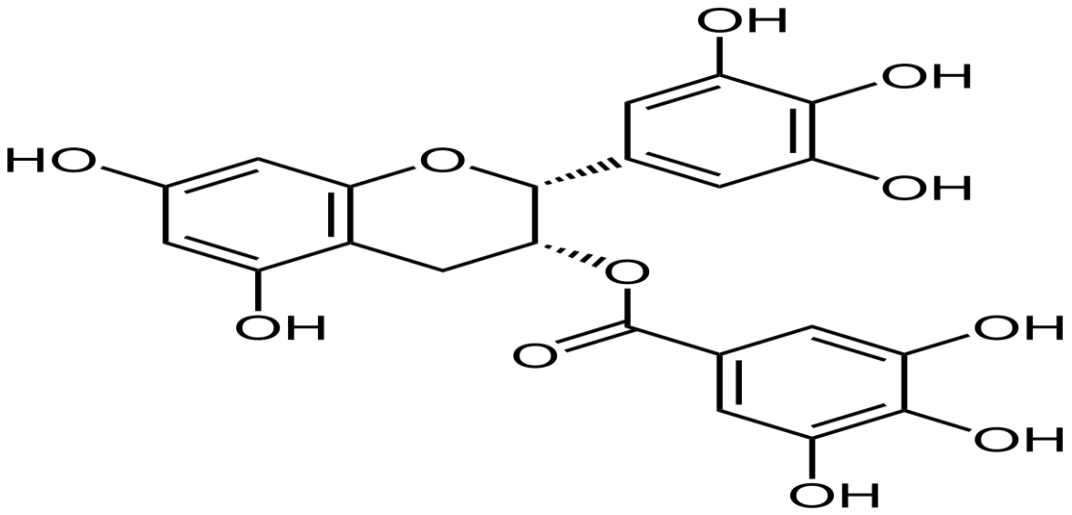


Figure 14. Epigallocatechin-3-gallate

2.9 Prescription medicines for the treatment of AD

Only a small number of medications have been reported to have a major impact on the physiology of amyloid peptide aggregation, despite enormous research into the pathophysiology and causation of AD. In clinical trials for the treatment of AD, four of the primary formulations, including injectable antibodies like Aducanumab, Gantenerumab, and BAN2401, and an orally administered small chemical named ALZ-801, have showed some promise[85]. The U.S. Food and Drug Administration (FDA) states that the majority of medications for AD fall into two categories: those that slow the advancement of the illness in persons who already have it and those that may temporarily relieve some of the disease's symptoms[86]. Drugs that function as glutamate regulators, cholinesterase inhibitors, or a mix of the two are included in the

latter category[87]. The following is a list of medications that could slow the disease's progression.

2.9.1 Aducanumab

It has an immunoglobin-based immunotherapeutic action in which fresh epitopes found in diseased amyloid aggregates activate human B cell clones[88]d. It demonstrates the varying levels of selectivity for insoluble plaques and fibrils as well as soluble amyloid oligomers[89,90]. Aducanumab was found to interact with the neurotoxic soluble amyloid oligomer when given intravenously[89]. Aducanumab is used to treat moderate cognitive impairment (MCI), and it was thought to be the first treatment to clear amyloid aggregates. Being a humanised antibody, it binds to amyloid oligomers that have accumulated with a high affinity and encourages their clearance through phagocytosis, which is mediated by Fc receptors[91]. A monthly dose of 10mg/kg administered intravenously had a positive impact on the cognitive endpoint of the Alzheimer's Disease Assessment Scale-cognitive scale (ADAS-cog) and the Clinical Dementia Rating -Sum of Boxes (CDR_SB)[92]. Furthermore, both tau PET imaging and phosphorylated tau (p-tau) in CSF showed a substantial biomarker impact. It has been stated that it takes five times as long for a drug to reach its peak in the brain as its plasma half-life or five times the dose interval[90]. The EMERGE phase 3 trials shown that an intravenous infusion of 10mg/kg monthly might significantly decrease the amyloid plaques in a dose-dependent manner. Aducanumab was also said to be able to lower CSF p tau, a biomarker linked to tau pathology and cognitive decline[92]. Amyloid-related imaging abnormalities with edema (ARIA-E) or microhaemorrhage (ARIA-H)116 were a serious side effect of using aducanumab[85]. By inducing microglial phagocytosis, aducanumab binding facilitates the removal of amyloid aggregates. It reaches the brain and decreases the soluble and insoluble A aggregates in a dose-dependent manner by binding with parenchymal A. The participation of microglia, which exhibits enhanced phagocytic activity by interacting with the Fc region of the antibody, was examined. Aducanumab reportedly boosted the recruitment of Iba-1-positive microglia to amyloid plaques. It was postulated that one potential route for the removal of A peptide aggregates would be Fc-mediated phagocytosis of antibody-amyloid complexes.

2.9.2 Gantenerumab

Fully human monoclonal antibody gantenerumab functions as an anti-amyloid IgG1 immunoglobin[93]. It binds to the amyloid species that have accumulated and removes

them by Fc receptor-mediated microglial phagocytosis, aiding in the neutralisation of oligomeric A42's in vivo neurotoxic impact[94–96]. Earlier phase 3 trials for gantenerumab, Scarlet RoAD (SR) and Marguerite RoAD (MR), investigated some of the lower dosage versions, including 105 and 225mg. Patients from two of the main patient categories participated in phase 3 AD research. Prodromal AD patients were retained in the SCarlet RoAD group, while mild AD patients were kept in the Marguerite RoAD group[93,96]. Numerous findings and arguments suggested that greater doses might exhibit clinical efficacy that was not clearly seen in earlier dosage studies[96]. Because of this, a positron emission tomography (PET) sub-study was created to examine the effectiveness of gantenerumab, which was up titrated to a dosage of 1200 mg in patients with prodromal to mild AD, on the A plaques as determined by florbetapir PET. After the medicine had been administered for 100 weeks, a dose-dependent clearance of the A plaques in the mice's brains was seen. A decrease in phosphorylated tau, total tau, and neurogranin levels in the cerebrospinal fluid (CSF) was one of the downstream pharmacodynamic effects that was also noticed. The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score and Functional Assessment Questionnaire results from a later post hoc subgroup analysis of patients suspected of fast progression in the SR group also suggested a dose-dependent slowing of decline in the AD scale cognitive subscale (ADAS-Cog)[97]. After two years of treatment with a 225mg SR dosage, the mean amyloid level was seen to fall by a total of three times, by 39 centroids in the first year and 59 centroids in the second[93]. Together, our findings demonstrated that higher gantenerumab doses have appreciable impacts on cognition and function in a patient with early-stage AD. In the Open-Label Extension (OLE) phase, a PET investigation for SR and MR was started to determine the pharmacodynamics and short- and long-term safety of gantenerumab[98]. This study revealed a significant correlation between higher OLE baseline amyloid levels and better amyloid decrease during the first year of treatment. The areas of the brain linked to AD showed a significant regional decline, with the anterior cingulate showing the largest regional reduction.

2.9.3 BAN2401

A fully humanised injectable antibody with a considerable impact on both clinical and biomarker outcomes is called Ban2401, commonly known as Lecanemab[85,97]. It partially eliminates the insoluble amyloid plaques while also targeting the oligomers. When compared to oligomers, which have a 10-fold higher selectivity, affinity for

monomers is substantially lower. As opposed to plaques, it preferentially targets the soluble protofibrils of the bigger oligomers. The degree of clinical efficacy is controlled by selectivity for A oligomers and brain exposure. BAN2401 accelerates the clearance of the aggregated amyloid by Fc receptor-mediated phagocytosis by binding to it with high affinity. For the ongoing phase 3 CLARITY AD trial, the maximal brain exposure was expected to be reached after 2.5 months of twice-monthly administration of 10 mg/kg[99]. When compared to aducanumab, the start of clinical efficacy with BAN2401 happened earlier because a titration period is not included. Additionally, it demonstrated a dose-dependent reduction in A plaque in phase 2 and phase 3 trials. Additionally, CSF p-tau was discovered to have decreased, and a significant impact on CSF-NfL, a downstream biomarker of neuronal damage, was noticed. A 12-month treatment with a 10mg/kg biweekly ED90 dose showed 64% probability to be better on ADCOMS compared with placebo by 25%, missing the primary outcome 135s threshold by 80%[100]. At 18 months, a 10 mg/kg twice-weekly Lecanemab regimen decreased brain amyloid by -0.306 SUVr units while demonstrating a drug placebo difference in favour of active therapy by 27% and 30% on ADCOMS, 56% and 47% on ADAS-Cog14, and 33% and 26% ON CDR_-SR versus placebo, according to Bayesian and frequentist analysis, respectively[100]. Lecanemab was well tolerated, and at a dose of 10 mg/kg twice weekly, the prevalence of amyloid-related imaging abnormalities edema/effusion was 9.9%[100]. 18-month A decrease in brain amyloid was seen, and this was followed by a consistent decline in clinical endpoints across a few clinical and biomarker endpoints, according to Bayesian and frequentist analysis. These findings collectively imply that BAN2401 may be an effective therapy option for the removal of amyloid. Additionally, compared to gantenerumab and aducanumab, the ARIA E rate was significantly lower (up to 10%). The Clarity AD Phase 3 Study is currently in progress.

2.9.4 ALZ-801

The most cutting-edge, tiny oral therapeutic molecule, ALZ-801, selectively interacts with a monomer and penetrate the blood-brain-barrier[85]. It stops the neurotoxic soluble amyloid oligomers and prevents their misfolding in a dose-dependent manner[101–103]. As a pro-drug for Tramiprosate, ALZ-801 combines Tramiprosate with valine for increased GI absorption and tolerability. It also has a shorter plasma half-life, which explains its 40% capacity to cross the blood-brain barrier[104]. It showed positive clinical results in the high-risk group of individuals who were homozygous for all four

apolipoprotein E (APOE4) alleles[105]. The pharmacokinetic characteristics of ALZ-80 ensures that the amyloid β oligomer is completely suppressed by the recommended clinical dose and explains why clinical efficiency in patients of AD treated with ALZ-801/Tramiprosate began sooner than with antibody treatment.

2.9.5 Donepezil

By resolving the difficulties associated with employing Tacrine and Physostigmine as an acetylcholinesterase inhibitor, Donepezil has been discovered[106]. Based on the cholinergic theory, the favourable pharmacokinetic, pharmacodynamic, and safety profile is attributed. The acetylcholinesterase inhibitor is a special piperidine-based compound that is non-competitive, and has a higher selectivity and lower affinity for butyrylcholinesterase, mostly found in the peripheral nervous system. The drug's higher tolerability, moderate adverse effects, longer half-life (70–80 hours), transitory nature, and cholinergic properties are what make it preferred to other acetylcholinesterase inhibitors[107]. Compared to other prospective medications, the drug's longer half-life ensures less frequent dosage. One of the drug's main benefits is that it does not require dosage adjustments for elderly patients, individuals with compensated liver cirrhosis, or patients with any forms of renal failure. It mostly affects the rat brain and hippocampus.

2.9.6 Rivastigmine

It is the only medication that blocks the brain's butrylcholinesterase and acetylcholinesterase enzymes[108]. In order to postpone the secretion of acetylcholinesterase into the synaptic-cleft, it is utilised to improve cholinergic neurotransmission in the brain[109]. Rivastigmine has a lesser risk of side effects and better action selectivity. Later, after 2007, a continuous transdermal patch was utilised for the delivery of formulation with dosages of 4.6, 9.5, and 17.7 mg/day[110]. The earlier trials tested capsules with a dosage of 12 mg/day. Rivastigmine was found to be helpful for persons with mild to moderate AD when administered daily at a dosage of 6 to 12 mg or 9.5 mg transdermally[111]. Although the efficacy in both situations is the same, transdermal patches were found to have fewer negative effects at this dosage than capsules. Rivastigmine is more readily available in transdermal and oral pill forms than other cholinesterase inhibitors, which helps it adhere more effectively and gives carers more satisfaction.

2.9.7 Galantamine

Galantamine, a cholinergic substance, reduces synaptic plasticity damage, cognitive decline, and neuroinflammation brought on by lipopolysaccharide (LPS)[112]. A significant pathophysiological state in the brains of AD patients has been identified as the aberrant quantity of LPS and the accompanying gram-negative bacteria[113]. The overexpression of CD11b, which is indicated by the activation of microglia during the development of the neurodegenerative disease, is enhanced by overactivated neuroglial cells such astrocytes and microglia. In the hippocampus of the mice exposed to LPS, treatment with Galantamine resulted in decreased expression of NFκ-B, astrocytes, and microglial markers including CD11b and GFAP as well as pro-inflammatory cytokines like IL-1, IL-6, and TNF[114–116]. It further reduced the loss of synapse-associated proteins like SYN and PSD-95 caused by LPS in the hippocampal region[112,117]. Galantamine's pharmacokinetic characteristics demonstrated higher blood-brain barrier penetration and a longer bioavailability of 5 to 7 hours in the hippocampus. It increases the secretion of Ach in the hippocampus because it is a central AChE inhibitor. Galantamine boosts the survival of mice by lowering the levels of TNF- and Il-6 in their serum. All these findings showed that Galantamine has potential as a therapeutic component for neuroinflammatory illnesses like AD.

2.9.8 Memantine

The cholinergic-theory postulates that decline in AD patients is significantly influenced by acetylcholine-containing cell dysfunction[118]. Along with the aforementioned theory, the prolonged activity of N – methyl - D-aspartate (NMDA) receptors caused by the overexcitation of the glutamatergic system results in excitotoxicity, which is known as one of the key factors in the pathogenesis of AD[119]. Serotonergic and cholinergic ion channel receptors are involved in memantine's subsidiary activities, which enhance memory and learning functions as well as its ability to be tolerated therapeutically[120]. The NMDA receptor is thought to be the memantine's primary target. Memantine-treated animal models have shown to significantly decrease the levels of plaque deposits in AD patients' brains and the levels of neuroinflammatory biomarkers. In the case of AD, it has been discovered that the combination of Memantine with other strong medications has a considerably more promising effect than Memantine monotherapy[121].

2.9.9 Oxiracetam

Being nootropic medication oxiracetam is being tested for its potential to treat cognitive impairment[122]. Oxiracetam has been demonstrated to boost memory and the recovery of cognitive functioning when infused into the cerebellum of a rat model of vascular dementia[123]. Additionally, it was noted that oxiracetam lessens the release of inflammatory cytokines in stroke-affected rats[121]. A 100 M (maximum concentration) of oxiracetam was utilised for all tests because it had the least or no cytotoxic effects compared to the control group even at the highest dose. According to the findings of these tests, oxiracetam decreased antibody-induced morphological alterations and increased phagocytosis in BV2 cells[124]. The compact, short BV2 cells altered into an elongated and expanded morphology when stimulated with amyloid-. The compact form of the cells was discovered to be dominant after oxiracetam therapy, indicating the favourable therapeutic impact of oxiracetam on amyloid-induced peptide. Further research revealed that 1L-1b mRNA levels and the expression of the inflammatory cytokines TNF-, IL-6, and 1L-1b were all downregulated by oxiracetam[125]. Prior oxiracetam therapy decreased 1L-1b and TNF- production. These findings demonstrated that ORC decreased the release of pro-inflammatory cytokines mediated by antibodies. Additionally, oxiracetam decreased the amount of antibody-induced overproduction of nitric oxide (iNOS) mRNA, which was markedly increased in response to amyloid- stimulation[122]. Together, these findings indicated that oxiracetam is a recognised therapeutic drug for reducing amyloid-mediated peptide growth that leads in a variety of neurological diseases.

2.10 Synergistic and combinatorial Drugs approach for neurodegenerative disease

Because there is such a high demand for the diagnosis and corresponding prognosis of diseases in elderly people, the AD cases with moderate to severe instances of Alzheimer's disease is increasing at a very rapid rate in today's world. Only five approved medications, including Namzaric (a combination of Memantine and Donepezil), despite a significant increase in cases[126]. Out of these five medications, four—Memantine, Rivastigmine, Galantamine, and Donepezil—have received EU approval. The fifth medication, used in combination therapy (CT), has received FDA approval[127–130]. Due to the disease's complex nature, monotherapy—the use of a single drug formulation—often entails a few limitations in the management of AD, including problems with efficacy, safety, and the alteration of the illness[131]. The drugs currently on the market were developed under the conventional drug discovery paradigm of "one molecule-one target," and they have demonstrated to be palliative[132]. An individual

treatment agent would only affect one target and might change the pathophysiology of the disease in a few ways, altering how it progresses. Although a single drug formulation can be used for therapy at larger dosages, it is more likely that doing so will result in significant side effects. Combination therapy was used to address the shortcomings of monotherapy treatments, creating a pharmacological formulation for the treatment of AD by combining many different medications. Combination therapy has now established itself as the Gold Standard for the treatment of AD and can be utilised to target several pathogenic processes[133].

AChE inhibitor and memantine were initially administered to AD patients, followed by the coadministration of additional standard and non-traditional treatment agents like Vitamin E and Ginkgo biloba that eventually led to effective solutions[134]. In the current investigation, we identified nine main medication combinations that are linked to several biological targets connected to AD therapies (mentioned in table 3). Acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), NMDAR (N-methyl-D-aspartate receptor), MAO A, and MAO B (monoamine oxidase A, B) were the most frequently targeted enzymes. Acetylcholine and butyrylcholine are broken down into the neurotransmitter by the cholinesterase enzymes AChE and BuChE. A significant function for inhibiting these enzymes in the treatment of AD. They convert MTPP into MPP+ by oxidation, which increases neurotoxicity. ROS are produced by MAO B as it oxidises the substrate. It has been discovered that the endogenous neurotoxic N-methyl(R) Salsolinol targets MAO-A, which is thought to be implicated in neuronal death[135].

According to the aforementioned findings, combination therapy, which combines different mechanisms of action to create an efficient pharmacological strategy, is more effective than monotherapy. By encouraging the synergistic and additive effects, combination therapy boosts a drug's effectiveness. Various neuroprotective activities that prolong the clinical improvements and eventually slow AD progression are a few of the additional benefits of combo therapy.

2.11 Multi-target-drug-ligand

All currently available medications are monofunctional, meaning they only affect one target out of a variety of targets[136]. These medications are discovered to be fundamentally insufficient for a complex disease like AD[132]. A single molecule may have several concurrent biological characteristics. It has been found that single multimodal medication therapy offers higher benefits than combination therapy. Thus, a "multi-target-directed-ligand" (MTDL) design technique, which was operating on a new paradigm in medicinal chemistry, had emerged. By fusing drug molecules with various pharmacophore subunits from known biologically active substances, MTDL are created[137]. The need for various effects displayed by a single drug formulation is answered by MTDL, which also avoids the difficulty of administering several single pharmacological entities with improved bioavailability, pharmacokinetics, and metabolism[138]. A much easier method is provided by MTDL. Additionally, the therapeutic regimen is highly rationalised in expectation of improved patient compliance, a crucial concern in AD, and the likelihood of drug interactions would be at a minimum[139]. It is frequently observed that as the drug's effectiveness increases in a dose-dependent manner, its tolerance tends to decline. As a result, researchers are focusing more on finding multi-target-directed ligands (MTDL) to create hybrid therapeutic molecules that may have an impact on numerous targets at once. Because of its MTDL design method, Memoquin, a recently discovered unique therapeutic molecule, found as a significant anti-AD treatment candidate. By slowing down the rate of Ach hydrolysis and speeding up Ach secretion in the synapses, the drug's design method aimed to restore the brain's cholinergic function that AD disease had adversely damaged[140]. This brand-new family of dual-binding site inhibitors that engage with both sites concurrently may lessen the cognitive loss in AD and target the disease's etiology[50,141,142]. Numerous in-vitro and in-vivo tests that take into consideration AChE inhibitors, A aggregation, antioxidant effects, and BACE-1 inhibition were carried out to show the many modes of action of Memoquin. The drug's in vitro profile comprised Memoquin’ s antioxidant properties, anti-AChE activity, anti-aggregating profile, and anti-BACE1 activity. On the other hand, Memoquin’ s in vivo performance profile comprised the capacity to reverse the cholinergic deficit, lower expression, and accumulation, lower hyperphosphorylation, and lower behavioural impairments.

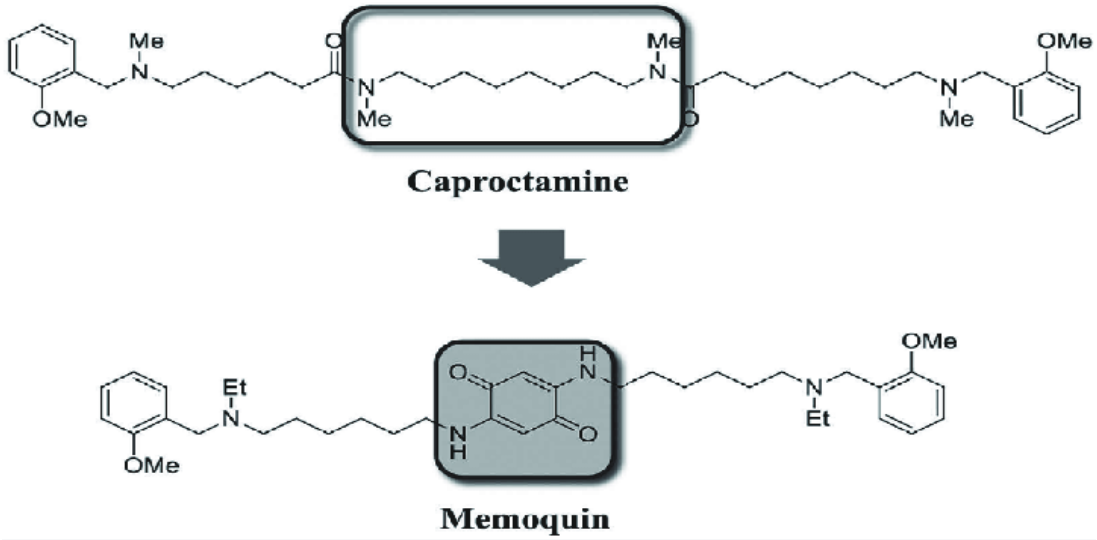


Figure 15. Design structure of Memoquin

3. METHODOLOGY

3.1 Exploration for potential therapeutic agent

Review of literature was performed for the search of potential therapeutic agents responsible for the clearance of amyloid β and the preventing NFT formation. From various literature and the database available online we found and listed few secondary metabolites, prescription drugs, new discovered synergistic and combinatorial drugs and suitable multi-target-drug-ligand based drugs. The databases and online journals used for the drug search were – PubMed, PubChem, Drugbank, ClinicalTrials.gov, U.S Food and Drug/ Drug approvals and database.

- For searching the list of drugs from PubMed, enter your search terms in the main search box at the top of the PubMed window, using synonyms, brackets, and Boolean operators, and then click the search button.
- Same procedure was done for searching the drug from PubChem as well.
- For searching the tools from clinicalTrial.gov database, we entered few query data such as- diseased condition and other terms (NCT number, drug name, investigator name) and hit enter. If specified data is required a specific region or country can also be entered in the search button.

Once the relevant drugs and other therapeutic agents were found they listed in the sorted manner in a excel sheet.

3.2 Target search drug molecules

The possible targets for the selected list of drugs were found using the Drugbank database (https://go.drugbank.com/). One target was picked out of all the targets for future research since it had inhibitory findings. Drugbank is an extensive online database with free access that contains details on the medications and the objectives that each one is intended to treat. It is a new tool for bioinformatics and cheminformatics that combines the chemical makeup of medicinal compounds with their thorough protein targets.. Following every two years, there are monthly updates and corrections to the data release schedule. More than 800 of the more than 4100 medicinal entities in the drug ban database are small compounds that have received FDA approval, The following steps were done for searching the suitable target of the drug-

- To search for the suitable targets of a drug molecule enter the name of the molecule in the search bar of database page and then hit the search button.

- Then go to the target section by scrolling the menu present at the left side of the page. Under the target section, look for various targets of the drug molecule having inhibitory effects.
- From the list of targets, one with suitable inhibitory effect was selected for docking with respective ligand molecule.

3.3 Exploring the novel therapeutic molecules having similar pharmacokinetic properties with known drugs for the treatment of AD.

Using PubChem database, we searched for the possible drug molecules having similar pharmacokinetic effects as of the known prescription drugs as listed in table 5. For different set of drugs different number of similar structures were found. A specific sorting and filtering criteria were chosen and applied for the suitable structure to be enlisted having therapeutic effect against AD. Two of the major parameters for sorting the list of similar structure were- heavy atom count, molecular weight count, complexity and the XLogP Value.

3.4 Evaluation of the pharmacokinetic characteristics of the potential drug molecules using SWISS ADME

All the ligand molecules or the potential drug molecules were accessed for their pharmacokinetic properties using SWISS ADME tool. It is an online tool for assessing the medicinal chemistry compatibility, drug-likeness, and pharmacokinetics of small compounds.

3.5 Structure retrieval of target molecules

The structure of the target molecules was retrieved from database called Uniprot (https://www.uniprot.org). The 3-dimensional structure of all the target molecules were saved in the .pdb format and processed for docking using Discovery Studio.

3.6 Target and Ligand Preparation

As a part of target preparation all the H_2O molecules and the ligands were deleted from the 3D structures and the final prepared structure was recorded in .pdb format. For preparing structure of ligand of all the drug were recorded in .mol2 format using discovery studio.

3.7 Blind docking

Swiss Dock is a online-based, open-access platform for protein and ligand docking.

3.8 Analysis of Target-ligand complex

All target-ligand interaction structures were saved in .chimera format when the docking process was completed. Utilising the Chimaera Software (Version 1.6) from UCSF, all interactions were examined.

3.9 Protein-protein interaction through STRING

Information from various sources, including as experimental data, computer study techniques, and collections of open text, is included in the STRING database. It is openly accessible and regularly updated. The database highlights functional enrichments in user-provided lists of proteins using different functional classification systems, including GO, Pfam, and KEGG. The most recent version 11b contains data on over 24,5 million proteins from more than 5000 distinct organisms. A group of academic firms, including CPR, EMBL, KU, SIB, TUD, and UZH, created STRING. Few significant interactions were seen in the PPI interaction between ACE and other AD-related genes.

The p-value for PPI enrichment was calculated using stat analysis on the STRING dataset and was found to be 1.0e-16. An average local clustering coefficient of 0.633 was discovered for the provided proteins. Edges represent connections between peptides. Pink and light-blue lines denote known interactions, green, red, and navy-blue lines denote speculated interactions, while yellow and black lines denote additional interactions. There were 39 total nodes and 190 total edges in the network. The findings demonstrated the significant connections between the ACE gene and other genes linked to Alzheimer's disease.

4. RESULTS AND DISCUSSION

4.1 Important therapeutic agents

From various literature sources and database, we found fifteen potential secondary metabolites having effective therapeutic role in the case of AD (listed in table 1).

Table 1. List of secondary metabolites with their target and mechanism of action.

S. No	Secondary Metabolite	Route of administration	Target	Signalling mechanism/Pathway	References
1	Gallic acid	Infused into hippocampus	Lys28-Ala42 salt bridge	• Breaking the salt bridge of amyloid β peptide. • Interaction among the -COOH cluster of the oxidized product and the ε-amino clustered Lys16 via Schiff base	[143]
2	Rosmarinic Acid	Oral	Dopaminergic synapse	• Increased secretion of dopamine and dopaminergic synapse pathway.	[144]

3	Salvianolic Acid B	Intraperitoneal	Hippocampus	• Hindered level. Of plasma lower-density lipoprotein cholesterol • Synthesis of enzyme secretase associated with amyloidogenic pathway.	64
4	Luteolin	Intraperitoneal	Hippocampus	• Induces changes consistent with GSK3 inhibition by decreasing amyloidogenic γ-secretase APP processing. • Promotes presenilin-1 (PS1) carboxyl-terminal fragment (CTF) phosphorylation. • Downregulates the utterance of NOS, MMP-9, COX-2, TNF-α, IL, and chemokines. • Modulates the activities of transcription factors such as CREB, Cjun, NRG-1, Nf-κB, p38, p53, AP-1, and β catenin. • It inhibits the functioning of various protein kinases.	64
5	Quercetin	Oral	Hippocampus	• Competitive inhibitor of AChE and Butyrylcholinesterase (BChE). • Reverses the Tau protein hyperphosphorylation via MAPKS and PI3K/AKT/GSK3β signalling pathway.	145
6	Fisetin	Oral	Hippocampus and Cortex	• Modulation of Cdk5/p53, restoring the synaptic proteins, • regulation of CREB, • AcetylCoA regulation, • degradation of NAD+, • regulation of advance glycation End products (AGE), • Fisetin-TFEB-MTORC1-Nrf2 linkage. • Modulation of Kelch-like-ECH-associated protein 1 (Keap1), Nuclear factor erythroid 2-related factor 2 (Nrf2), and Antioxidant response elements (ARE) pathway.	146
7	Myricetin	Oral	Hippocampus	• Hindering the β-secretase-1 and •Enhancing the levels of α-secretase and decomposing the APP competitively.	147
8	Dihydromyricetin	Oral	Hippocampus	• Restoration of gephyrin to the normal level • Hindering the production of β-secretase.	54
9	Silibinin	intraperitoneally	Hippocampus and Cortex	• Reducing the activity and amount of acetylcholinesterase, • Enhanced synaptic protection, gliogenesis, and neurogenesis.	72
10	Oleuropein	Oral	Hippocampus	• Radical scavenging activity.	74
11	Rutin	Oral	Microglia and astrocyte	• Inhibition of glial cell activation and attenuation of the production of inflammatory cytokinin.	76
12	Curcumin	Intraperitoneal	Hippocampus	• Reduces the utterance of γ secretase component presenilin-2. • Helps in the concentration of enzymes that degrades beta-amyloid.	55
13	Crocin	Oral	Blood-brain Barrier	• Enhanced expression of neprilysin (NEP). • upregulated ApoE clearance pathway.	82
14	Cryptotanshinone	Oral	Hippocampus and Cortex	• Upregulation of α-secretase.	148
15	Epigallocatechin-3-gallate	Intraperitoneal	Hippocampus and Cortex	• Inactivation of the TNF α/JNK signalling pathway to attenuate the insulin resistance.	149

From the database such PubChem and PubMed and clinicaltrial.gov we found almost nine potential drug molecules which have passed clinical trials and are used for the treatment of AD also called prescription drugs (listed in table 2).

Table 2. List of prescription drugs available for treatment of AD

S. No	Drug	Molecular Target	Mechanism of action	Indication	Clinical Status
1	Aducanumab	Human B cell clones	immunoglobin-based immunotherapeutic. action	AD	FDA Approved
2	Gantenerumab	Accumulated peptide	anti-amyloid IgG1 immunoglobin	AD	FDA Approved
3	BAN2401	Soluble protofibrils of the bigger oligomers	Fc receptor-mediated phagocytosis	AD	FDA Approved
4	ALZ-801	Amyloid β oligomer	It stops the neurotoxic soluble amyloid. oligomers and prevents their misfolding. in a dose-dependent manner	AD	FDA Approved
5	Donepezil	Acetylcholinesterase	acetylcholinesterase inhibitor	AD	FDA Approved
6	Rivastigmine	Butrylcholinesterase and acetylcholinesterase	blocks the brain's butrylcholinesterase. and acetylcholinesterase enzymes	AD	FDA Approved
7	Galantamine	Cholinergic target	reduces synaptic plasticity damage, cognitive decline, and neuroinflammation brought on by lipopolysaccharide (LPS).	AD	FDA Approved
8	Memantine	NMDA receptor	Modulation of serotonergic and cholinergic ion channel receptors	AD	FDA Approved
9	Oxiracetam	1L-1b mRNA , inflammatory cytokines TNF-, IL-6, and 1L-1b	It decreased antibody-induced morphological alterations and increased phagocytosis in BV2 cells	AD	FDA Approved

Apart from these two classes of therapeutic agents we have found few of the recently discovered combinatorial drugs having synergistic and combinatorial effect which (listed in table 3).

Table 3. List of synergistic and combinatorial drugs

S. No	Molecular Target	Drug	Mechanism of action	Indication	Clinical Status	Reference
1	SIRT1	Cilostazol+Aripiprazol+Donepezil	• Expressional modulation of AD-related genes such as GSK-3β, and P300. • Synergistically increase the acetylcholine release. • Increases the neurite length and improved cell viability.	AD	FDA approved	[150]
2	Mitochondria	Dihydropyrimidine-Thiones+ Clioquinol	• Decrease in Aβ-levels and restore the functional vesical trafficking based on metal binding.	NDD	FDA approved	[151]
3	AChE receptor and Nicotinic receptor	Galantamine + Memantine	• Shows neuroprotective role against glutamate toxicity through activation of nicotinic AChE receptor.	AD	FDA approved	[131]
4	Extra synaptic NMDAR	Memantine + Nitro-glycerine (Nitromemantine)	• Elevated the synaptic and dendritic density. • Reversed the lost connection of the brain and restored the normal number of synapses.	AD	FDA approved	[136–138]

5	ACE Receptor	Donepezil + Clioquinol	• In-vitro ,showed better antioxidant properties, • Chelating properties of Zn (II) & Cu (II), • AChE properties, and ability to penetrate the Blood-brain barrier.	AD	FDA approved	139,142,152
6	AChE, BuChE and MOA B	Rivastigmine+ Rasagiline (Ladostigil)	• The combined effect of AChE inhibitor and anti-monoamine oxidase B. • Antioxidant properties scavenge the activity of free radicals. • Reduces the concentration of halo-amyloid precursor protein (APP). • Increases the concentration of protein kinase C.	AD, PD, LBD.	FDA approved	50,141,142
7	MAO A and MAO B	VK-28 + Propargylamine	• Specifically halts the MAO A and MAO B activity in the brain.	AD, PD	FDA Approved.	135,150,153
8	AChE receptor+	Donepezil + Memantine	• Significant enhancement in SIB. • Less decline in ADCS-ADL and improvement in CIBIC.	AD	FDA Approved	121
9	Ache, BuChE, NMDA	Rivastigmine+ Memantine	• Cholinesterase inhibitor and NMDA receptor antagonist.	AD	FDA Approved	151

4.2 Target for drug molecules

Using Drugbank database all the possible targets of nine potential drug molecules were found and listed in table below.

Table 4. List potential drugs and their respective targets.

S.No	Drug	Brand Name	Target	Action
1	Aducanumab	Aduhelm	Amyloid beta A4 protein	Antagonist Binder Antibody
2	Gantenerumab	Gantenerumab	Amyloid beta A4 protein	Antagonist Binder Antibody
3	BAN2401	Leqembi	Amyloid beta A4 protein	Binder
4	ALZ-801	Alzheon	Amyloid beta A4 protein	Antiboanti-oligomer and aggregation inhibitory
5	Donepezil	*Adlarity, Aricept, Namzaric*	Acetylcholinesterase	Inhibitor
			Tumour necrosis factor-inducible gene 6 protein	Inhibitor
			Interleukin-1 beta,	Inhibitor, Inducer
			Nuclear factor NF-kappa-B (Protein Group)	Inhibitor
			NMDA receptor (Protein Group),	Down regulator
6		Exelon, Nimvastid, Prometax	Acetylcholinesterase	Inhibitor
			Cholinesterase	Inhibitor

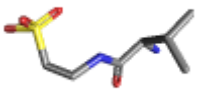
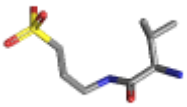
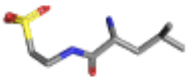
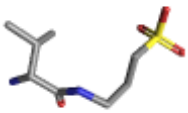
7	Galantamine	*Razadyne*	Acetylcholinesterase	Inhibitor
			Cholinesterase	Inhibitor
8	Memantine	*Axura, Ebixa, Marixino,*	Glutamate (NMDA) receptor (Protein Group)	Antagonist
			Glycine receptors (Protein Group)	Inhibitor
9	Oxiracetam	Oxiracetam	AMPA receptor	Allosteric Modulators

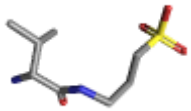
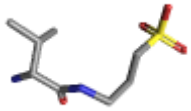
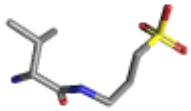
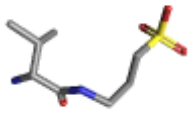
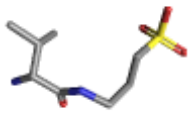
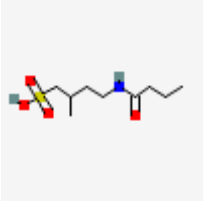
4.3 Similar structured novel therapeutic molecules

Using PubChem database, we searched for the drug molecules having structure similar to the known drugs and found various novel molecules having possible therapeutic effect for AD. These structures are mentioned in the table.

4.3.1 ALZ-801

Table 5. Structure similar to parent drug ALZ-801

S.No	Parent Drug	Similar Structure Compound CID	Structure
01	Alz-801	14332601	
		25008296	
		54245797	
		54443792	
		162475925	

		162475926	
		162475929	
		162475931	
		162475931	
		162475934	
		163493486	

4.3.2 Donepezil

Table 6. Structure similar to parent drug Donepezil

S.No	Parent Drug	Similar structures Compound CID	Structure

01	Donepezil	3152	
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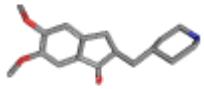
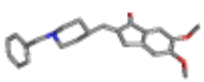
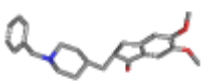
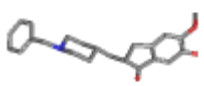
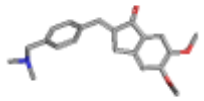
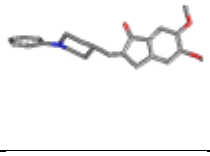
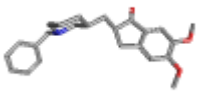
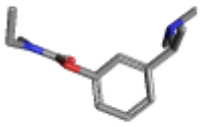
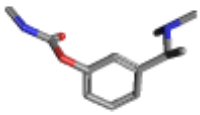
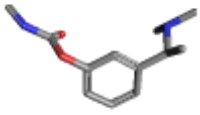
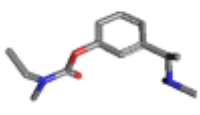
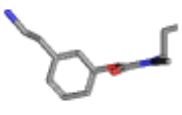
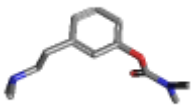
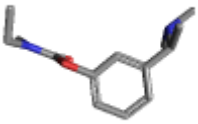
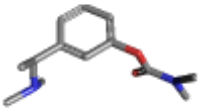
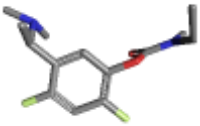
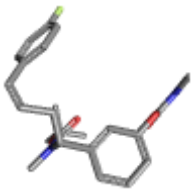
		1150567	
		10446897	
		10762160	
		11697764	
		14553555	
		25197364	

		46889411	
		129824804	

4.3.3 Rivastigmine

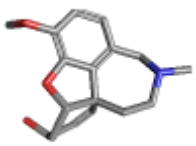
Table 7. Structure similar to parent drug Rivastigmine

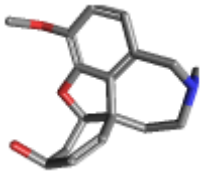
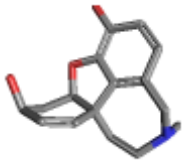
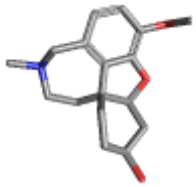
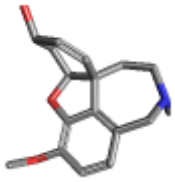
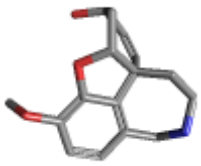
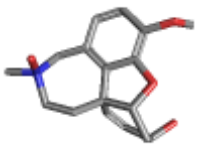
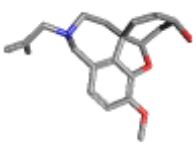
S.No	Parent Drug	Similar Structure	Structure
01	Rivastigmine	5077	
		46092	
		46093	
		77991	
		10978630	

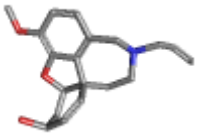
		11097701	
		12133267	
		23645310	
		144027474	
		145778378	

4.3.4 Galantamine

Table 8. Structure similar to parent drug Galantamine

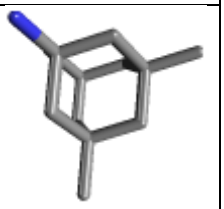
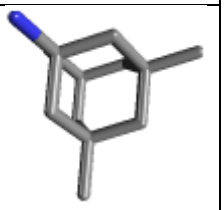
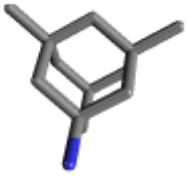
S.No	Parent Drug	Similar Structure Compound CID	Structure
	Galantamine	3449	

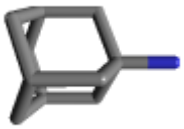
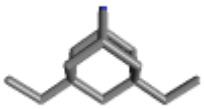
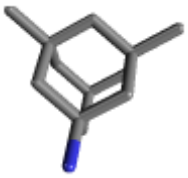
		9651	
		121587	
		443722	
		443723	
		676392	
		9838394	
		11748698	
		24863955	

		44447598	

4.3.5 Memantine

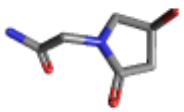
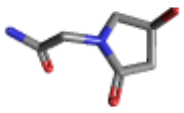
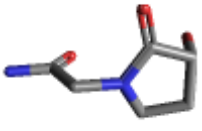
Table 9. Structure similar to parent drug Memantine

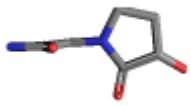
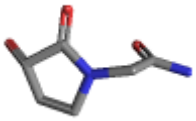
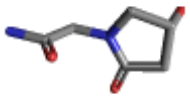
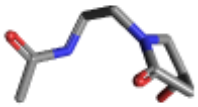
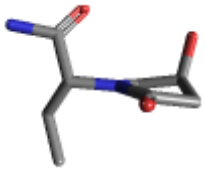
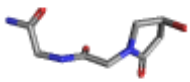
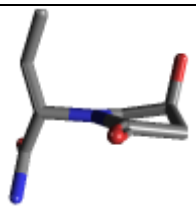
S.no	Parent drug	Similar structure Compound CID	Structure
01	Memantine	2130	
		4054	
		64150	
		181458	
		1263681	
		3010140	

		3776755	
		10013264	
		11229655	
		12377357	

4.3.6 Oxiracetam

Table 10. Structure similar to parent drug Oxiracetam

S.no	Parent drug	Similar structure Compound CID	Structure
	Oxiracetam	4626	
		3051965	
		3069834	

		3069835	
		3069854	
		6603951	
		10176428	
		11298370	
		11701304	
		15974796	

4.4 Pharmacokinetic properties

Pharmacokinetic properties of the potential drug candidates were analysed by SWISS ADME. All the important pharmacokinetic properties are listed in the table below.

Table 11. Pharmacokinetic properties of various drugs

S. No	Drug	Lipophilicity (Log $P_{o/w}$ (XLOGP3)	Water Solubility	Pharmacokinetics		
				GI absorption	BBB permeant	Log Kp (skin permeation)
01	ALZ-801	-3.04	2.58e+01 mg/ml ; 1.08e-01 mol/l	High	No	-9.91 cm/s
02	Donepezil	4.28	4.78e-05 mg/ml ; 1.26e-07 mol/l	High	Yes	-5.58 cm/s
03	Rivastigmine	2.29	1.76e-01 mg/ml ; 7.01e-04 mol/l	High	Yes	-6.20 cm/s
04	Galantamine	2.81	4.06e-01 mg/ml ; 1.10e-03 mol/l	High	Yes	-6.55 cm/s
05	Memantine	3.28	2.85e-01 mg/ml ; 1.59e-03 mol/l	High	Yes	-5.06 cm/s
06	Oxiracetam	-2.24	6.43e+02 mg/ml ; 4.06e+00 mol/l	Low	No	-8.86 cm/s

The schematic representation for the SWISS ADME analysis of the potential drug molecules is given in the figure.

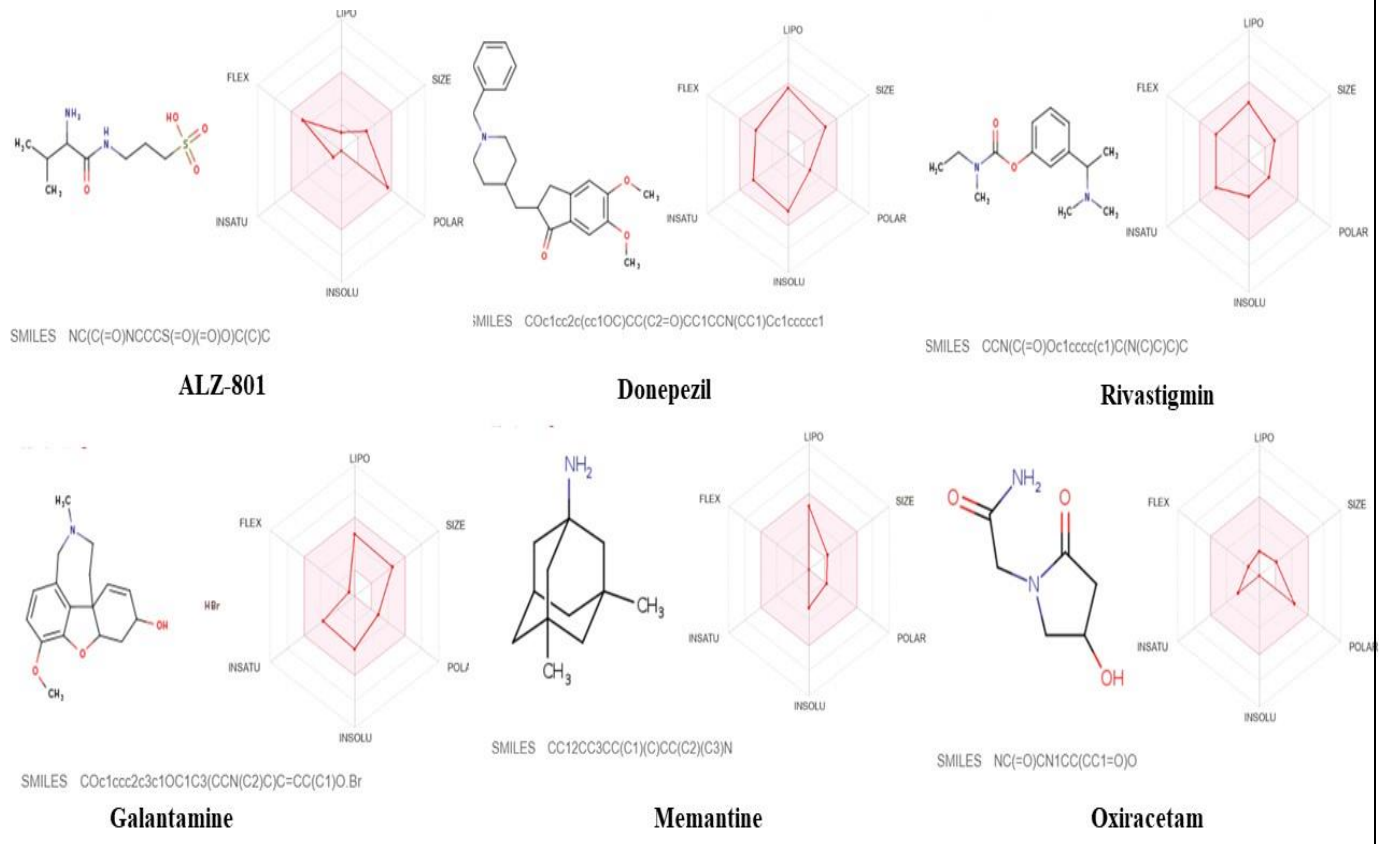


Figure 17. SWISS ADME analysis for various drugs

4.5 Blind Docking using SWISS DOCK

From the docking of various therapeutic agents with potential target related in the AD pathology we have curated a list of drug molecules in the table below.

Table 12. Binding energy of various drugs with their respective targets

S.No	Target	Drug	Binding Energy (kcal/mol)
01	Amyloid β A4 protein	Aducanumab	-10.3
02	Amyloid β A4 protein	Gantenerumab	-10.1
03	Amyloid β A4 protein	ALZ-801	-10.1
04	Acetylcholinesterase	Donepezil	-7.53
05	Acetylcholinesterase	Rivastigmine	-10.2
06	Acetylcholinesterase	Galantamine	-10.1
07	NMDA Receptor	Memantine	-10.2
08	AMPA Rece[tor	Oxiracetam	-10.1

4.6 Protein-protein Interaction through STRING

4.6.1 PPI analysis for amyloid β A4 target

Few significant interactions were seen in the PPI interaction between amyloid β A4 and other AD-related genes. The p-value for PPI enrichment was calculated using stat analysis on the STRING dataset and was found to be 2.95e-07. An average local clustering coefficient of 0.792 was discovered for the provided proteins. Edges represent connections between proteins. Figure 18 illustrates known interactions as pink and light blue lines, predicted interactions as green, red, and navy-blue lines, and additional interactions as yellow and black lines. There were 11 total nodes and 32 total edges in the network. The findings demonstrated the significant connections between the amyloid β A4 target and other genes linked to Alzheimer's disease.

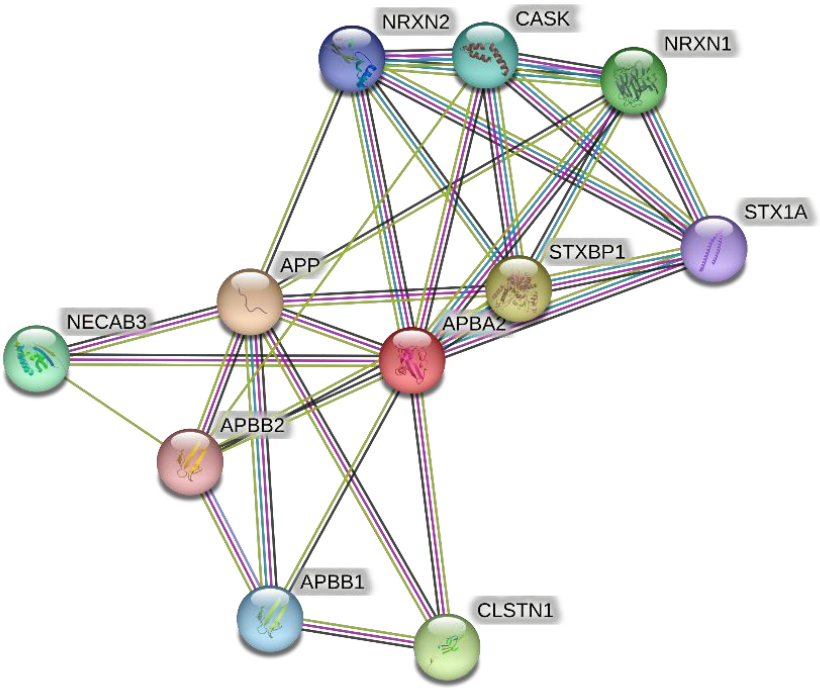


Figure 18. Protein-protein interaction for amyloid β A4 target

4.6.2 PPI analysis for acetylcholinesterase receptor

Few significant interactions were seen in the PPI interaction between acetylcholinesterase receptor and other AD-related genes. The p-value for PPI enrichment was calculated using stat analysis on the STRING dataset and was found to be 0.000196. An average local clustering coefficient of 0.785 was discovered for the provided proteins. Edges represent connections between proteins. Figure 19 illustrates known interactions as magenta and light blue coloured lines, predicted interaction as red, green and navy-blue lines, and additional interactions as yellow and black lines. There were 11 total nodes and 25 total edges in the network. The findings demonstrated the significant connections between the amyloid β A4 target and other genes linked to Alzheimer's disease.

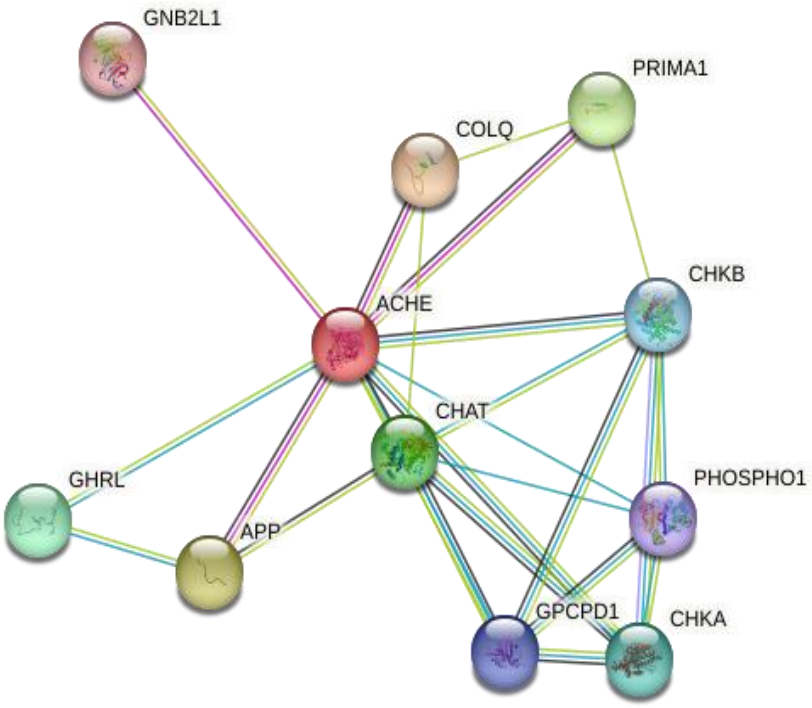


Figure 19. Protein-protein interaction for acetylcholinesterase receptor

5. Conclusion

The most common neurodegenerative diseases is AD. It is the sixth most common reason for death. However, current evidence indicates that it might come in as high as third for older adults, right behind cancer and heart disorders. The aberrant build-up of amyloid peptides in the CNS is now understood to be the root cause of the disease. The primary reason for the build-up of this undesirable peptide is a disturbed equilibrium between the generation and clearance of amyloid. AD is regarded as a neuroendocrine illness known as "Type 3 Diabetes" because it has few traits in common with type 1 and type 2 diabetes. Numerous pathways, including GSK 3, MAPK, Wnt, and C-JNK pathways, are disrupted as a result of the blood sugar levels' rapid changes. These messed-up metabolic processes result in insulin resistance, which exacerbates dementia. Even with an enormous increment in the cases of AD patients around the world, the number of medications available to treat the condition is still extremely small. Only four main medications are known to be effective at significantly reducing AD symptoms as of right now. Aducanumab, Gantenerumab, and BAN201 are three of these four subclasses, which are injectable antibodies. ALZ-801, the fourth subclass, is an oral medication. These medications have a great deal of

promise to reduce the symptoms, but they also have some very substantial adverse effects, including headache, confusion, agitation, and dizziness. Studies on secondary metabolites derived from plants that have anti-aggregating effects for amyloid have revealed some intriguing characteristics, including the capacity to traverse the blood-brain barrier, a longer serum half-life, improved absorption, and other desirable pharmacokinetics characteristics.

In the later phases of the disease, medicines or pharmacologically active substances are needed because they have fast responses that plant-based metabolites do not have. The present medicine molecules, on the other side, have so many adverse effects, as was already described. In order to combat the rising number of instances of Alzheimer's disease, it became necessary to find potential therapeutic molecules or a combination of such molecules. When the many potential combinations of the available medications were evaluated on the mouse model, a new method known as synergistic and combinatorial drug formulation was developed. . Combinatorial and synergistic medication formulations demonstrated superior amyloid aggregation inhibition as compared to monotherapy. Additionally, the use of combinatorial medication therapy also helped to lessen the negative effects that were brought on by monotherapy, which involves using only one dose of a single therapeutic molecule.

In order to target numerous sites with a single therapeutic formulation, a novel strategy known as a "multi-target-directed ligand" (MTDL) design strategy was created. Single multimodal medications have been demonstrated to outperform combination therapy in terms of benefits. In contrast to combinatorial therapy, the MTDL class of medications meets the desire for various effects displayed by a single pharmacological formulation with only a single dosage. Additionally, the MTDL strategy would greatly reduce the likelihood of drug-drug interactions.

We can draw the conclusion that the aforementioned groups of current therapeutic modalities for AD are appropriate for treating AD or any other neurodegenerative illness which depends on the phase of the disease and the patient's physical condition. An easy intake of pants-based secondary metabolites can aid in the disease's recovery in the early stages when symptoms are not very noticeable. Advanced stages, however, necessitate the use of synergistic and combinatorial drug molecules since they have a much faster response time than secondary metabolites or ordinary drug molecules.

Given the therapeutic approach's current perspective, a deeper comprehension of the drug combinations' synergistic effects on the treatment of AD is important. As a result, a more thorough investigation that includes clinical trials and validations is crucial to the project's future direction.

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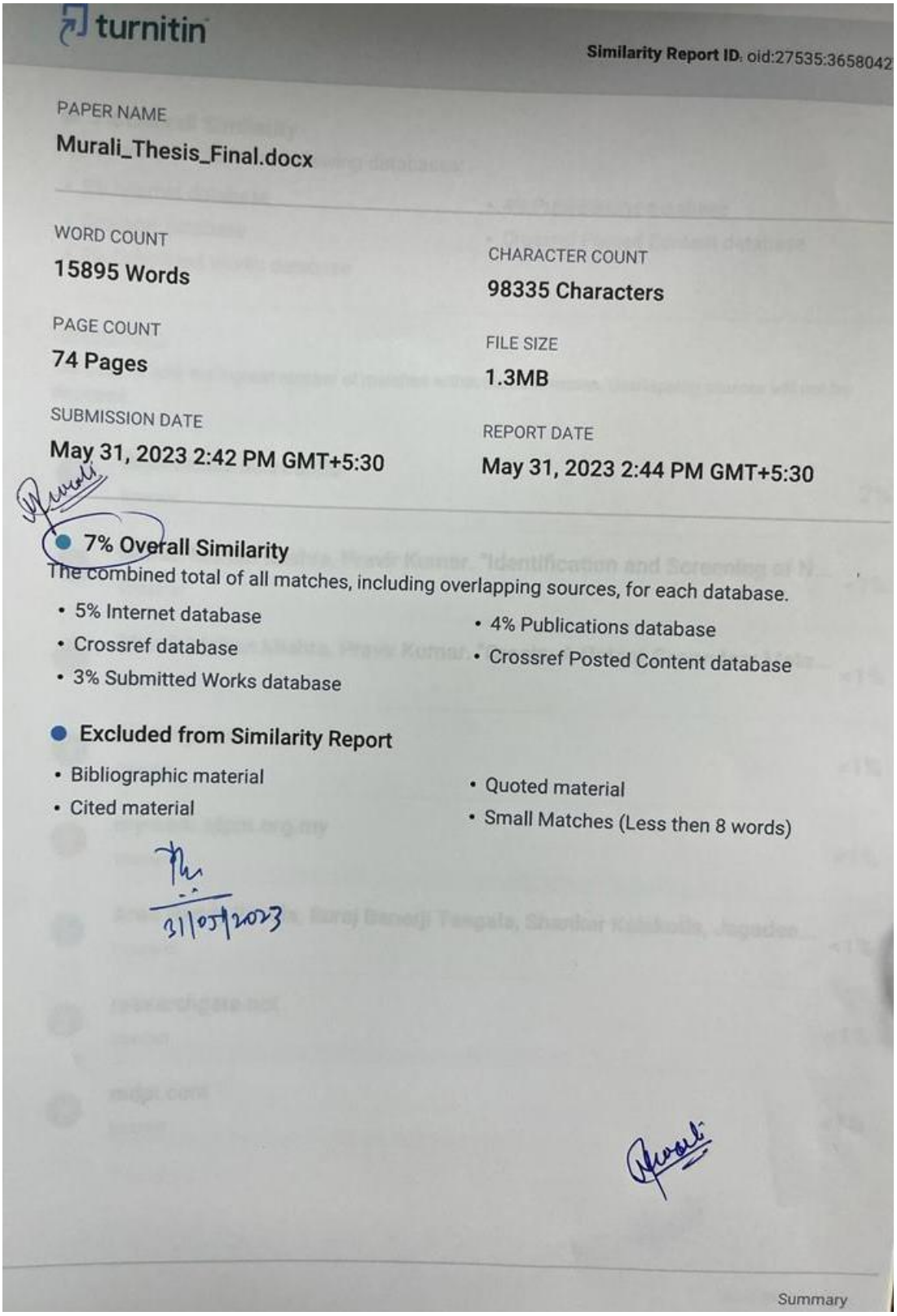

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