

MOLECULAR DOCKING AND ADMET STUDY OF COUMARINS EXPLORING THEIR POTENTIAL AS TREATMENTS FOR ALZHEIMER 'S DISEASE

***Devendra Kumar**

India.

Article Received on 15 October 2026,
Article Revised on 05 October 2026,
Article Published on 16 October 2026,

<https://doi.org/10.5281/zenodo.23385063>

***Corresponding Author**

Devendra Kumar

India.



How to cite this Article: *Devendra Kumar. (2026). Molecular Docking And Admet Study Of Coumarins Exploring Their Potential As Treatments For Alzheimer 'S Disease. World Journal of Pharmaceutical Research, 15(20), 655-705.

This work is licensed under Creative Commons Attribution 4.0 International license.

1. INTRODUCTION

Alzheimer's disease (AD) is a neurological illness that affects older individuals and manifests as memory loss, cognitive decline, and linguistic impairment. As per the cholinergic theory, AD is mostly associated with a drop in acetylcholine (AChE) levels in the brain due to damage to cholinergic neurons. Therefore, increasing AChE with acetylcholinesterase inhibition is one of the most effective ways to treat AD symptoms. **Sonmez et al.**^[42] A class of physical and cognitive impairments known as neurodegenerative diseases are brought on by the death of brain neurons. The most prevalent ND, Alzheimer's disease has been diagnosed in over 30 million people worldwide. Its symptoms, which start with recurrent short-term memory loss and advance to the degradation of

higher cognitive skills including language and decision-making, are progressive and permanent. The disease has a significant social and economic impact because of the nature of these symptoms. This neurodegeneration is the consequence of several interconnected pathways supported by genetic and environmental variables rather than a single cause or process. Treatment has become challenging because of this intricate pathophysiology, and the medications currently on the market mainly relieve symptoms. **Mzezewa et al.**^[33] Alois Alzheimer, a German neuro scientist, told about the Alzheimer's disease in 1907. One of his patients had cognitive impairment, behavioral issues, and memory loss. Deficiencies. A biopsy revealed significant brain damage, including ageing plaques, neuron muddle known as neurofibrillary Muddle and axis. lack of Nerve cell and synapses, primarily in the hippocampus and neocortex association regions. The Pathophysiology of Alzheimer's disease

begins with hippocampal shrinkage About 80% of people 65 and older have Alzheimer's; dementia only affects a small percentage of people at this age, but the frequency of dementia in Alzheimer's rises to 25% in people 80 and older. In older adults, Alzheimer's disease (AD) is the most common cause of dementia., and it is typified by growing neurological changes. **De et al.**^[12]

The death of brain neurons causes a class of cognitive and motor problems known as neurodegenerative diseases (NDs). Over 30 M Population worldwide have been identified with AD. It starts with recurrent temporary memory loss and leads to the declined of higher cognitive skills, including language and decision-making. Its symptoms are gradual and irreversible. Because of the nature of these manifestations, the illness has a significant social and economic impact. The coumarin scaffold possesses numerous inherent pharmacological characteristics, and because of its inherent ChE and MAO inhibitory potential and ease of functionalization, coumarin Products have shown assurance as a foundation for MTDL Structure efforts. Therefore, by creating and synthesizing a short line of Legands with Exchange of moieties known to increase prohibition of the MAO and cholinesterase enzymes, this study sought to addition investigate the strength of coumarin compounds. **Breijyeh et al.**^[8]

1.1. Epidemiology of Alzheimer

One of the main reason of dependency, deformity, and Mortality, which is explained as obtained continuing cognitive intellectual disability severe enough to affect day-to-day functioning. According to current estimates, there are 44 million dementia sufferers in the world today. As the inhabitant ages, this is predicted more than triple 2050, Mental illness is the Main cause of Death in England and Wales, Explanation for 11.6% of all recorded deaths in 2015. It is undefined which reason of mental illness are reducing, but Present research indicates the occurrence of mental illness, especially in mens, may be set down in Western countries. It supported by upgrade vascular risk control. Low- and middle-income nations, which exhibit trends of rising diabetes, hypertension, and cardiovascular illness, are envisage to see the most increase in Mental problem prevalence in the upcoming years 50% to 75% of dementia cases are caused AD. **Lane et al.**^[31]

1.1.1. Alzheimer's disease Stages

The presymptomatic stages, which can increase for several many years, is one of the clinical trail of AD. At this condition, no use full disability in regular activities, any indicators and

manifestations of AD, and minimal memory loss along with early pathological changes in the cortex and hippocampus. (2) The mild or early stage of AD, This condition occurs when a variety of symptoms begin to appear in patients, including mood swings, the onset of depression, confusion about time and place, and difficulties with daily life due to memory loss and lack of focus. (3) Moderate AD stage, where the illness progresses to parts of the cerebral cortex, leading to a lack of impulse control, difficulty reading, writing, and speaking, and significant memory loss with difficulties recognising friends and family. (4) Serious AD, also defined as last - stage, is distinguished by a critical buildup of neuritic plaques. Sufferer may become disable and feeling complications with engulf and urination, which ultimately result in their death. **Breijyeh Z, et al.**^[08]

1.1.2. Risk factors and causes of AD

Growing older, genetics, brain trauma, and vascular diseases, infections, and Ecological Elements are some of the risk factors linked to Alzheimer's disease. Now It is unclear what is the cause of pathological alterations in Alzheimer's disease. Although a no of explanation have been Proposed to describe AD, some contend that makes daviation in the synthesis and refining of amyloid protein serve as the primary initiating factor, while others maintained that cholinergic disorder is a significant threat factor for AD. However, there is currently no recognised theory to define the pathophysiology of AD. **Breijyeh Z, et al.**^[08]

1.2 Natural Compounds Used for the Treatment of AD

It is believed that medicinal herbs have been used since the dawn of humanity. Since the 19th century, these plants have been used to extract their pure active ingredients and make medications. Numerous secondary metabolites have been discovered to date and are available for use and study in the pharmaceutical sector. **Jamkhande et. al.**^[25]

We looked at the consequences of auraptene, an inhibitor of novel acetylcholinesterase with H₂O₂- pramoted cell death in PC12 cells. AD is a advancing and declining deformation of the CNS, that's linked to cognitive and memory impairment. **Hadipour et al.**^[23]

In vitro, it was discovered that coumarins, a class of naturally occurring secondary metabolites, improve glucose absorption by activating the PI3K and AMPK pathways, lowering blood Sugar levels, and increasing insulin Responsiveness. Numerous medicinal plants contain the furanocoumarin bergapten, which has been demonstrated to have antidepressant, inflammatory-reducing and antioxidant qualities. **Salem et al.**^[40]

Elderly patients who have few drug-placebo differences in adverse events or significant adverse events can safely use brexpiprazole. Participants who took brexpiprazole experienced greater somnolence and extrapyramidal symptoms, which should be closely watched when administering this medication to elderly patients who exhibit agitation linked to AD-related dementia. **Zhong et al.**^[50]

A vast family of substances with either synthetic or natural origins are known as coumarins. In the natural world, coumarins are present in microbes and plants. Dicoumarol's anticoagulant and anti-inflammatory activities are well known, and other authors have reviewed them. It has also been noted in recent years to have additional significant bioactive properties. It is essential to talk about the chemistry of things in order to better comprehend them. bthe chemical in connection with its biological characteristics. **Silva et al.**^[41]

Leukocyte relocation and sensitivity signalling pathways are two immunological responses that are crucially regulated by the chemokine receptor CCR1. Acute pulmonary swelling, including hyper inflammatory reactions in SAARC COV-19 patients, autoimmune diseases, and chronic inflammatory diseases, has all been linked to CCR1 dys regulation. Natural chemicals offer an untapped resource for medicinal development because of their diverse structural makeup and multifunctional biological activity. Among these, the coumarin derivative esculin has encouraging antioxidant and anti-inflammatory qualities. The exact chemical processes by which esculin interacts with CCR1 are still unknown, though. **Agrawal et al.**^[2]

The evolutionary process of natural sources like plants, marine organisms, and fungi produces natural products, which are chemical compounds. Many of these compounds have been refined through the selection processes of coevolution between the species that produce them and their predators. Since ancient times, people have utilized these natural substances to treat and cure a variety of illnesses. Many medical advances are based on natural ingredients, and the usage of these substances has been shown to be the most effective method for discovering new medications. **De Sousa NF et al.**^[12]

A tertiary alkaloid medication called galantamine hydrobromide has been created and authorized for use in treating gentle -to-Restrained AD in a no. of countries, including the United state of America and many European nations. Galantamine acts in 2 effective ways. The medication now on the market is a reversible therapy for AD inhibitor of competition of

acetylcholinesterase that has shown effectiveness as a modulator of allosterism of nAChRs..
Lilienfeld et al.^[30]

According to earlier research, coumarins have a broad spectrum of biological functions, making them the most popular scaffold for creating new medications. A significant class of natural substances, coumarins are added to food and cosmetic products. Antibacterial, antioxidant, anti-inflammatory, anticoagulant, anti-tuberculosis, anticancer, and anti-AD properties have all been documented for coumarin. A pyrone ring with a fused benzene, which acts as the structural nucleus, make up the structure of coumarin. Research has indicated that both chemically manufactured and naturally occurring coumarin analogs have strong AChE inhibitory action. **Kamarudin et al.**^[27]

1.3. TOOLS

In silico studies of CADD are increasingly used in industry and academia. These technologies aid in drug development by representing and manipulating molecular structures, calculating descriptors and properties, building models, and providing computational support. Understanding the molecular connection between qualitative and quantitative perspectives is crucial. **Sousa et al.**^[45]

A virtual screening method based on pharmacophores was used to identify the naturally occurring coumarin scopoletin as an blocker of AChE. Using a variety of experimental techniques, including behavior studies, LTP tests in hippocampus pieces, and measurements of newly Produces ACh in synaptic vesicles, the capacity of SCT as a pro cholinergic and cognition-improving therapy was examined in greater detail in this work. With a well-structured dosage result curve, SCT increased the K-stimulated release of ACh from rat frontal cortex synaptic vesicles. **Hornick et al.**^[21]

CADD, This is a major obstacle to the creation of new medications and ultimately becomes a social problem because of its ability to help reduce the vast no. of medical needs. Although, the use of CADD. The use of CADD technologies at various stages of the drug invention process lowers this overall cost. Because of this, CADD techniques are becoming more and more common. Over the past few decades, they have been essential in the development of substances that have therapeutic significance. They are mostly used in the pre-clinical stage, despite the fact that their application in clinical phases is showing increasing potential. of possible atoms to direct the optimization of compounds. Ligand-Based and Structure-Based

techniques are frequently distinguished based on the kind of input molecule. A key element of structure-based methods for synthesis or shield of possible modulators, then it will be converted into hit compounds is a target's (3D) structure. A collection of compounds with different moiety and known potencies are taken into consideration by the ligand-based approach, which creates theoretical prediction models to, for example, find chemical bio mimetic Molecules to a known substrate blocker, are drug. The chosen compounds' efficacy, selectiveness, and ADMET features are further improve to develop compounds, which are later confirmed in vitro and in vivo to become drugs. **Llorach-Pares et al.**^[32]

Chemical structures and the outcomes of biological testing are publicly available at PubChem (<http://pubchem.ncbi.nlm.nih.gov>). It began as a research project under the NIH Molecular Libraries Roadmap Initiative in September 2004. PubChem offers three related datasets: BioAssay, Compound and Substance. The Material database Provide sample Elucidation from depositors, while the Molecular data consists novel chemical compositions obtained from the substance depositions. **Wang et al.**^[49]

We provide the completely automated and user-friendly protein–ligand interaction profiler software (PLIP) for unchangeable and open excesses. Since PLIP complements other cutting-edge online products like SwissDock, GalaxySite, or ProBiS., it can also be utilized for drug design, docking result evaluation, combining site likeness assessment, and drug reprofiling. Protein-ligand interaction patterns can be thoroughly identified and visualized using the PLIP web service. **Salentin et al.**^[44]

Protox III Analyzing the toxicity of a chemical or medicine is a crucial stage in its design. Additionally, regulatory decision-making organizations like the FDA and EMA should "embrace" the green chemistry paradigm and recognize the significance of The ProTox 3.0 web server's intuitive design is self-explanatory and may be utilized for the toxicological assessment of these compounds with little to no assistance. Its design makes it easy to operate. The user can provide the PubChem name or the canonical SMILES string of the input compound to conduct a prediction on the server. The chemical's structure is depicted in the drawing window according to user preferences. Even what you might consider to be the speculative substances before they are created in the lab can be predicted. **Banerjee et al.**^[4]

The PyMOL is a pictorial system for customizing and visualizing compounds was first made available in 2000 and was created by Warren Lyford DeLano. After Warren DeLano passed

away too soon in 2009, PyMOL was procured by Schrödinger Inc. which offered Preservation and access to new characterises at profit while preserving the original author's open-source ethos. PyMOL is a open-source, proprietary software program that is evolve, maintained and facilitated by Schrödinger. which also maintains licensing rights. **Rosignoli. et al.**^[38]

A variety of rapid yet accurate predictive models for pharmacokinetics, physicochemical properties, drug-likeness, and medicinal chemistry friendliness are available for free through the new SwissADME web service. These models incorporate proprietary expert approaches such as BOILEDegg and Bioavailability Radar. An intuitive user interface through the <http://www.swissadme.ch> website, which does not require a login, ensures simple, efficient input and interpretation. **Daina et al.**^[13]

The first method for docking flexible ligands to proteins was AutoDock, which was initially presented thirty years ago. Biomolecular structure prediction methods were occasionally severely limited by the limited storage capacity and processing speed of the then-emerging computer infrastructure. Strong molecular dynamics methods such as AMBER 1 were limited to short time scales and typically only looked at small convolutional spaces around a starting model, even if they offered a physics-based representation. The novel DOCK method employed a simplified depiction of ligand-receptor interactions, with stiff ligands and a sphere-based mechanism for scoring interactions, to search the wider conformational regions required for computer docking research and drug development. **Goodsell et al.**^[16]

1.4. Obstacles in the Creation of Therapies Based on Natural Compounds

Despite the promising nature of natural chemicals, several challenges remain before they can be widely adopted as a treatment for Alzheimer's disease.

1.4.1. Uniformity

Standardization of extracts derived from natural sources is one of the main obstacles. Factors including the plant's geographic origin, crop time, and extraction techniques can all have a significant impact on the stability and structure of the final extracts. This type of variability could lead to disparate safety and efficacy profiles. Therefore, standardizing extraction and purification processes is crucial to ensuring consistent treatment outcomes. **Taylor et al.**^[46]

1.4.2. Toxicity and Safety

Thorough scientific investigation is necessary to assess the toxicity profiles of natural substances, despite the fact that their historical use frequently leads to the notion that they are safe. In order to identify potential adverse effects and determine safe dosage levels, comprehensive preclinical and clinical toxicity studies must be conducted. Without this knowledge, the potential for unforeseen negative consequences remains a significant barrier to clinical application. **Bunch et al.**^[7]

1.4.3. Clinical Experiments

The transition from in vitro research to clinical usage is a time-consuming and resource-intensive process. Clinical trials are necessary for natural compounds that show promise in lab settings to confirm their safety and efficacy in human populations. These trials require substantial funding, carefully planned research, and collaboration between academic institutions, industry partners, and regulatory agencies. **Ruiz et al.**^[38]

1.4.4. Regulatory Obstacles

Navigating the regulatory landscape to get novel medications based on natural ingredients approved could be challenging. To pass regulatory bodies, a novel medicine needs to have a substantial body of evidence demonstrating its efficacy and safety. Because natural extracts are complex and may include multiple active components, complying with these requirements poses unique challenges. The development of natural chemicals in standardized medications that adhere to current good manufacturing practices (CGMP) regulations is equally significant. Separation and Description It takes a thorough phytochemical analysis to separate and identify certain chemicals having anti-filarial qualities. High-performance liquid chromatography (HPLC) and mass spectrometry (MS), two sophisticated analytical methods, are useful instruments for examining these substances and establishing the connection between their chemical makeup and biological function. **Taylor et al.**^[46]

1.4.5. Mechanistic Research

To fully utilize these natural chemicals' medicinal potential, it is crucial to comprehend the precise process by which they intensify their effects. In order to identify particular pathways influencing these compounds, future research should make use of molecular biology and biotechnology methods. The knowledge gained from these mechanical investigations can guide the logical creation of stronger derivatives or artificial analogs. **Sonmez et al.**^[42]

1.4.6. Formulation and Distribution

Enhancing the stability and bioavailability of natural chemicals through effective formulations is another primary area of research interest. Nanotechnology-based delivery systems, like polymer nanoposomes and liposomes, can help make these medications work better in the body and reduce their harmful effects. **Taylor et al.**^[46]

1.4.7. Synergistic Combinations

Better outcomes could be obtained by looking at the potential synergistic effects of combining natural substances with already employed medicinal techniques. By reducing the dosage of each component, combination medicines can maximize therapeutic efficacy while minimizing unwanted effects. **Wanji et al.**^[48]

LITERATURE REVIEW

2.1. Literature Review on Alzheimer

Orioli et al. (2024) told about the primary characteristic of NDs is their intricate etiology, which includes several seemingly unconnected and as-yet-unidentified neural pathways and targets. Consequently, it seems that the "one target, one molecule" approach is ineffective in influencing the advancement. of complex multifactorial illnesses, and the creation of single molecular entities capable of concurrently modulating various biological targets implicated in their start and progression represents a more viable approach. The design of hybrid compounds, which are produced by combining various chemical moieties working through various pathways and exerting complementary and synergistic activities, is the primary foundation of this polypharmacological approach. The selection of a suitable main scaffold that may be readily and differently altered becomes crucial in this regard. In medicinal chemistry, coumarins are naturally occurring favored structures that serve as appropriate scaffolds for the creation of new multifunctional molecules for the treatment of ND. **Orioli et al.**^[36]

Joshi et al. (2021) firstly, coumarin was synthesized, and its capacity to inhibit thiadiazole or oxadiazole derivatives was assessed. Treat Alzheimer's disease by inhibiting acetylcholinesterase. Derivative design was first developed using in silico research and a review of the literature. Compounds were then created, described, and ultimately examined in vitro for anti-Alzheimer action. According to the in silico molecular docking study, molecules are successfully attaching to the AChE enzyme's CAS and PAS sites. Additionally, these investigations provide evidence that thiadiazole series chemicals are superior to

oxadiazole series molecules, namely The AChE enzyme is effectively inhibited by compounds that contain halogen and dimethyl amino substitutions. Clinical trials and commercialization require a forward-looking strategy. **Joshi et al.**^[24]

Salem et. al (2021) was studies enhanced cognitive performance and histological profile in this study highlight the neuro-protective potential of PDE5I, TAD and furano coumarin in an AD disease. TAD and BG's neuroprotective effects may stem from reducing neuroinflammation and controlling the crosstalk. The possibility using TAD or BG to treat AD-related cognitive and memory impairments is strongly encouraged by this work. **Salem et al.**^[40]

Kate Zhong et al. (2024) studied the three Phase 3 trials' data consistently demonstrate that patients taking brexpiprazole saw noticeably higher reduction in agitation than those taking a placebo. The dosage of 1 mg did not work. There was no drug-placebo difference in the flexible-dose study; post examination of dose groups revealed that agitation was significantly reduced in those getting 2 mg/d but not in those receiving lower doses. Elderly patients who have few drug-placebo differences in adverse events or significant adverse events can safely use brexpiprazole. Participants who took brexpiprazole experienced greater somnolence and extra pyramidal symptoms, which should be closely watched when administering this medication to elderly patients who exhibit agitation linked to AD-related dementia. Post-marketing studies should closely monitor deaths due to the documented excess of mortality in elderly individuals with schizophrenia treated with antipsychotics that resemble brexpipraz. **Kate Zhong et al.**^[50]

Feinsteina.et. al. (2019) discovered that whereas racemic BDF has intermediate potency, the LD 50 of BDF -cis in rats was approximately 50% below that of BDF-trans. BDF-cis has a extended half-life in rabbits than BDF-trans, which may explain partly due to its elevated toxicity. Last but not least, weakened the total NADH dependent reductive capability of cultivated SH-SY5Y human neuroblastoma cells, indicating a decrease in cellular metabolic activities. When combined, these findings imply that variations in the relative optical isomers levels found in the monetarily available Preparation may be somewhat responsible for the various lethal signs of BDF poisoning. **Feinsteina.et. al.**^[15]

Silva et al. (2022) Numerous investigations were conducted in order to generate dicoumarol, a symmetrical natural biscoumarin with significant pharmacological activity. effective

techniques for the synthesis of it and its derivatives, as well as the examination of their bioactivities. The most promising synthetic techniques are those that employ green solvents and heterogeneous catalysis, which offer financial benefits because the catalyst can be recovered and reused and are also more environmentally friendly. **Silva et al.**^[41]

2.2. Literature Review On Natural Compounds

Lilienfeld et al. (2002) discovered for AD patients, galantamine is a well-tolerated and efficient therapy. In important regions of AD, it consistently offers wide-ranging, long-lasting, and clinically meaningful improvements. The remarkable effectiveness profile of galantamine may be explained by its distinct dual mode of action. **Lilienfeld et al.**^[30]

Farihi et. al. (2023) told about psychotropic plants and their neuroprotective compounds has advanced significantly in the last few decades. In preclinical research, several natural substances have demonstrated significant promise in the management of Alzheimer's disease. Patients must exercise caution when using phytomedicines, nevertheless, because not all natural chemicals are completely safe. Although encouraging outcomes have been seen in animal models, it is impossible to assure the security of treatment in people. Inhibiting cholinesterase has become a successful treatment approach for neurodegenerative diseases, such as Alzheimer's. According to our study's results, each of the seven substances under investigation may one day be used as an oral treatment. Notably, gedunin has the highest binding affinity when compared to the commonly used inhibitor, although fisetin and berberine also show respectable binding affinities for acetyl cholinesterase. This demonstrates gedunin's potential as a strong acetyl cholinesterase inhibitor. **Farihi et. al.**^[15]

Rogawski et al. (2003) has been clearly proven to work well and be safe for treating symptoms of AD and other types of major neurocognitive discord, based on a lot of clinical experience. The system by which Although the exact mechanism by which memantine produces its positive clinical effects is unknown, nearly forty years of thorough research have shown that neurotransmitter-gated ionotropic receptors, NMDA receptors, and potentially 5-HT₃ serotonin and nicotinic acetylcholine receptors are the only confirmed molecular targets that are likely to be significant at therapeutic doses. Although memantine's ability to block NMDA receptors has been well studied, it is still unclear how disrupting NMDA receptor function results in a reduction in symptoms. **Rogawski et al.**^[37]

Huang et. al. (2021) We showed that IMP reduces 2VO-induced cognitive decline and hippocampal neuron damage. Its mode of action is probably because it controls pro- and antiapoptotic biomarkers, enhances hippocampal synaptic ultrastructural alterations, lengthens SAZ and PSD thickness, and increases the amount of PSD-95. These results show that IMP is a promising neuroprotective drug against different neurodegenerative disorders and offer a fresh viewpoint on the course of VD sickness. **Huang et. al.**^[22]

Hornick et al. (2011) demonstrated that the coumarin SCT increases LTP in the CA1 region of the hippocampus, amplifies ACh release that is dependent on presynaptic activity, and exerts cognitive enhancing qualities in mice with aging and cognitive impairment. We believe SCT improves NMDA-dependent LTP by acting as an agonist at nAChRs. **Hornick et al.**^[21]

Esra Ucar et al. (2018), studied findings demonstrated the biological activity of *P. orientalis* water and methanol extracts. The extracts' chemical makeup was made clear. via GC-MS. The study's findings demonstrated that both extracts effectively inhibit the enzymes α -glucosidase, α -amylase, AChE, and BuChE. It is important to note that at the same concentration level, both methanol and water extracts showed more α -glucosidase and α -amylase inhibitory action than the antidiabetic medication acarbose. The leaf extracts' antibacterial, anticancer, and antioxidant properties are all very encouraging. To sum up, these findings show that the different *P. orientalis* L. leaf extracts. Preparing pharmaceutical formulations to treat a range of illnesses, including diabetes, cancer, Alzheimer's disease, and others, may benefit from the usage of leaves. Our laboratory is conducting additional research in this area. **Esra Ucar et al.**^[47]

Amin et al. (2020) Test elements were molecularly docked in the active pocket of the quorum-sensing regulators CviR as well as the transcriptional regulators LasR and PqsE Except for asacoumarin A, all of the chemicals bind. however, feselol, a similar molecule, binds inside both receptors. However, asacoumarin A's extra oxygen group at carbon 6 might be the cause of its inactivity. Based on previous findings, chain E was chosen for docking. The transcript controller LasR exists in homo-tetramer form. The test chemicals' binding interactions with one another Both LeadIT and Discovery Studio were used to view the amino acid residues inside the transcriptional controller LasR's active site. Both 2D and 3D molecular interactions are used to display the findings. **Amin et al.**^[1]

Hindam et al. (2020) The results of this study demonstrate that umbelliferone and xanthotoxin protect rats from STZ-induced cognitive impairment. This impact may be at least partially explained by downregulating the expression of NF- κ B p65 and COX II, suppressing acetylcholinesterase, and reducing neuroinflammatory response, oxidative stress, and neuronal death. **Hindam et al.**^[18]

Bunch et al.(2016) When compared to similar patients on warfarin anticoagulation for other reasons, the presence of AF dramatically raises the risk of dementia, including Alzheimer's disease. Nonetheless, both AF and non-AF patients' quality and effectiveness of anticoagulation treatment, as measured by percent TTR, continue to be significant risk factors for dementia. **Bunch et al.**^[7]

Ruiz et al. (2018) Edoxaban is more affordable than warfarin for community-dwelling tolerant mild AD. DOACs are not cost-effective, despite the fact that patients with reasonable to extreme AD living in the community and patients with AD at any stage residing in a long-term care facility may experience favorable clinical outcomes from anticoagulation medication. in contrast to warfarin for these groups. **Ruiz et al.**^[39]

Kimura et. al. (2002) he was created the GITA Model, which includes the hepatic first-pass metabolism, absorption, and GI transit processes. The significance of GI transit rate in determining the bioavailability of medications taken orally was evident from assessments of the absorption kinetics of pharmaceuticals with different absorption characteristics based on the GITA Model. Additionally, the GITA Model allows for the prediction of drug absorption behavior, including the plasma concentration-time profile following oral delivery to rats and humans. Kimura et. al.(2002).^[26]

Chen et al. (2018) Dermal absorption's capacity for both naturally occurring ,artificially produced compounds is commonly quantitatively described by the Kp, or pace at which substances enter the stratum corneum However, the Kp's regulatory implementation in standard development is usually impeded by the absence of empirically determined Kp values that follow regular and standardized procedures. This result indicated that other physicochemical characteristics, rather than only molecular weight, should be used to understand the impact of molecule size on chemical skin penetration. In situations where experimentally derived Kp values are not easily accessible. **Chen et al. (2018).**^[9]

Walters et al. (2012) Our Kp model identified a sub-domain of molecular properties that were initially reported to describe a compound's properties for the first time in the QSAR literature. antineoplastic similarity as a key element in a solute's ability to pass through the epidermal membrane. This result indicated that other physicochemical characteristics, rather than only molecular weight, should be used to understand the impact of molecule size on chemical skin penetration. In situations where experimentally derived Kp values are not easily accessible. **Walters et al. (2012).**^[39]

Nisha et al. (2016) according to this comparing and evaluating every parameter, our admetSAR investigation showed that acylguanidine 7a may be predicted to be a strong BACE 1 inhibitor. Its ADMET characteristics showed a lot of similarities to our control, MK-8931, which is now undergoing an advanced clinical trial. Out of all the factors, tartaric acid has the lowest LD50 value, making it the least appropriate. In conclusion, acylguanidine 7a and pioglitazone are strong, selective, orally accessible, and nontoxic β -secretase inhibitors that may make excellent foundation drug candidates. **Nisha et al. (2016).**^[34]

2.3. CADD Tool

Bitew et al. (2021) The pharmacokinetic, drug-likeness, and toxicity profiles of sixteen flavonoid derivatives as well as two control medications were presented in this work. The findings indicate that chrysin, wogonin, baicalein, logP, and logS are all suitable and have high HIA values. apigenin and genistein, indicating reduced toxicity and improved absorption. were anticipated to be carcinogenic. Except for eriodyctiol, which interacts with P-gp, the majority of the compounds are likely to be CYP3A probes. Among the examined flavonoid derivatives, butein and morin were found to be immunotoxins, while baicalein and quercetin were found to be mutagenic, according to toxicological endpoints prediction analysis,. **Bitew et al.**^[5]

Choong et. al. (2010) Numerous medications have demonstrated enantioselectivity in P-gp activity, either through preferential transport of a single enantiomer or by varying inhibitory potencies towards P-gp activity between enantiomers. This may lead to varying quantities of a single enantiomer in the brain, which could affect the central action of chiral medications. Different pharmacological reactions have been linked to a number of ABCB1 polymorphisms. Future clinical research on this topic will be difficult because it is still unknown how the ABCB1 polymorphism may affect the enantioselectivity of P-gp activity and the enantiomer brain distribution. **Choong et. al.**^[10]

Banerjee et. al. (2018) Protox-III is an open-access computational toxicology platform that uses 33 distinct models to predict significant hazardous effects. Classifying predictions in many toxicity levels, such as oral poisoning, organ-specific poisoning (such liver toxicity), and other hazardous closing points including mutation, carcinogens, cytotoxicity, and immunotoxicity, is one feature of the improved protox-III website. Similarity-based cluster cross-satisfaction is integrated with molecular equality, piece phenomenon patterns, frequently seen features, and the piece utilizing machine learning. It also discusses the molecular objectives and toxicity path, offering important information about the possible mechanism underlying harmful responses. **Banerjee et. al.**^[4]

Borul et al. (2022) said that Several chemical characteristics, such as molecular loads, molygapy, topological polar surface zones (TPSA), solubility, and drug-likeness ratings, were used to assess the synthesized compounds. Their MOLLOGP value ranges from 0.74 to 3.28, and their molecular load ranges from 118 to 298. The compounds' medications ranged from -0.80 to -2.04. This study evaluated the possible applicability of synthesized compounds for medication development while taking into account their dependability. Through strategic partnerships, the lead discovery with medicine and biotechnology firms offers software solutions and services in areas including enterprise data management, cheminformatics, bioinformatics, molecular modeling, and lead discovery. **Borul et al.**^[6]

Huey et al. (2012) To estimate the interactions between small molecules, such as possible medications or substrates, and a receptor with a known three-dimensional structure, a set of automated docking tools has been created **Huey et al.**^[19]

Sebastian et al.(2015) Protein Ligand Interaction Profiler: A crucial component of structural biology, medication creation, and biological research comprehends how proteins and ligands interact. Despite its significance, the scientific community has access to free, complete equipment. The primary non-coordinating interaction in the protein-ligand complex can be automatically identified and visualized in three dimensions using this platform. Protein data bank files or ligands from the user-defined complex, like molecular docking, are among the different input. **Sebastian et al.**^[44]

Borul et al. (2022) The molecular properties of the generated compounds were investigated in the present work. TPSA, solubility, weight, mole logp, and drug-likeness score. The mollogp values of synthetic substances range from 0.74 to 3.28, and their molecular weights

range from 118 to 298. The drug-likeness scores of the substances range from -0.80 to -2.04. **Borul et al.**^[6]

Rosignoli et al. (2022) notes that CPA pipeline construction is made simpler by interoperable software and tools. The usability of several algorithms with applications in this field is limited because they only offer a command-line interface. Make use of your computational biology expertise. Scientists will have a wide range of possibilities as new in-silico techniques become available as computer power and accuracy increase. A platform called PyMOL combines molecular imaging with CPA. The flexible platform PyMOL can be accessible through plugins. **Rosignoli et al.**^[38]

Goodsell et al. (2020) He was claims that the AutoDock suite is scalable and modular to support continued research into the accuracy and utility of docking devices. We think the AutoDock Suite will continue to gain from advancements in the industry, particularly in modeling accuracy, which have been made feasible by notable advances in processing power in recent years. Early compute limits will be lifted thanks to the massive boost provided by accelerated architectures like GPUs, which will enable more costly and precise energy estimations. **Goodsell et al.**^[16]

Daina et al. (2017) has discovered For one or more compounds, the SwissADME Web tool computes critical physicochemical, pharmacokinetic, and drug-related properties. Embedding free, publicly available prediction models that showed statistical significance, predictive power, easy translation to molecular design, and intuitive interpretation were among the backend goals. Through interactive features, the latter enables simple input and effective output analysis without the need for prior CADD knowledge. **Daina et al.**^[13]

Kim et al. (2015) is saying In this publication, the PubChem Substance and Compound databases are given. Data contributors provided their own information to the Substance database. The standardization process involves extracting unique chemical structures from the Substance database and writing them as records in the Compound database. This offers a comprehensive perspective on data related to a specific structure. **Kim et al.**^[52]

Kaushik et al. (2015) explained that ChemDraw and ChemSketch are the most powerful chemical drawing programs currently on the market. ChemDraw and ChemSketch are quite similar. ChemSketch can be used to create intricate drawings with easily comprehensible

graphical elements. Perhaps use Advantage or ChemDraw to construct from templates. Chemistry 4-D Draw offers pre-made templates for a variety of ring systems, amino acids, and carbohydrates in addition to ChemBio Draw. **Kaushik et al.**^[19]

Altschul et al.(2005) Compositional score matrix adjustment, he claims, was first created to compare sequences with highly biased compositions. It might be useful to utilize it everywhere. Our findings suggest that compositional changes may contribute to protein database similarity searches in general. The BLAST database search program's retrieval results are improved by adding compositional adjustment at a low execution time cost. **Altschul et al.**^[3]

2.4. AIMS AND OBJECTIVE

Molecular Docking and ADMET Study of Coumarins: Exploring Their Potential as Treatments for Alzheimer's Disease

The objective of this work is to search for potential naturally occurring substances with activity against Alzheimer disease, a neurodegenerative disorder. Pharmacokinetics and toxicity profiles of selected drugs will also be evaluated based on ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis. To aid in future development as anti- Alzheimer drugs, this combined analysis is used in prioritizing bioactive nature's products compounds which showed high binding affinity, drug-likeness and safety qualities.

2.5. Plan of Work

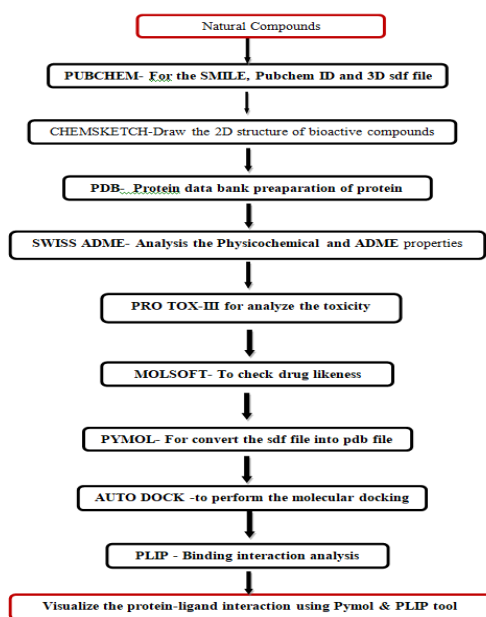


Fig. 2.1: Flow charts of Plan of work.

METHODOLOGY

3.1. Collection of Bioactive Constituents

Difenacoum (Pubchem cId-54676884), Umbelliferone (Pubchem cId-5281426), Esculetin (Pubchem cId-5281416), Aesculin (Pubchem cId-5281417), Fraxetin (Pubchem cId-5273569), Dicoumerol (Pubchem cId-54676038), Psoralidin (Pubchem cId-5281806), Auraptene (Pubchem cId-1550607), 6-Hydroxy-4-methylcoumarin (Pubchem cId-75409), IMPERATORIN (Pubchem cId-10212), Bergapten (Pubchem cId-2355), Xanthotoxin (Pubchem cId-4114), Deltoin (Pubchem cId-906525), Daphnetin (Pubchem cId-5273569), Osthole (Pubchem cId-10228), Warfarin (Pubchem cId-54678486), Scopolamine (Pubchem cId-5280460), Brodifacoum (Pubchem cId-54680676), Bromadiolone (Pubchem cId-54680085), Seselin (Pubchem cId-68229), Phellopterin (Pubchem cId-98608), citropten (Pubchem cId-2775), Daphnetin (Pubchem cId-5280569),

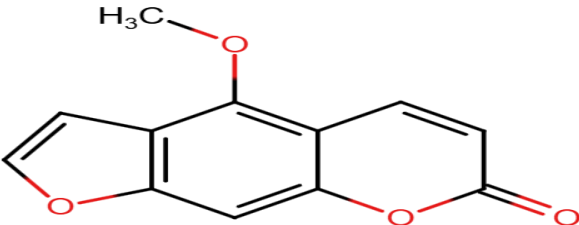
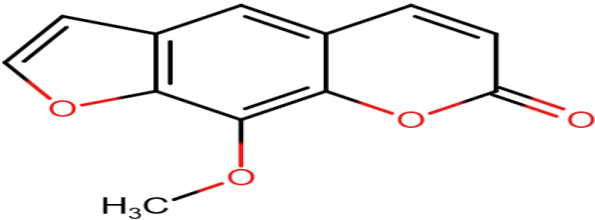
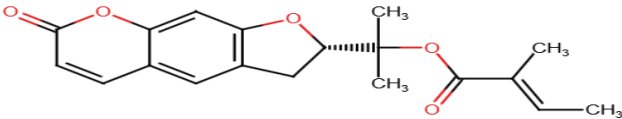
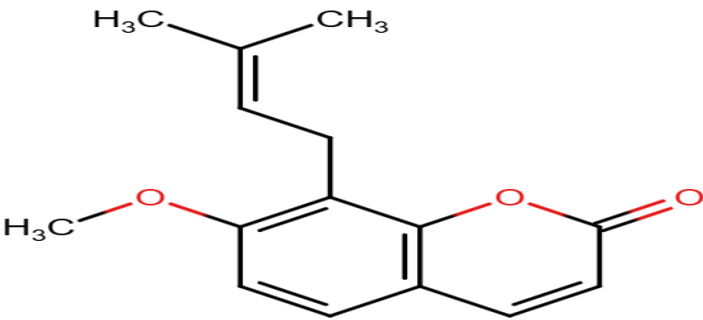
To choose the bioactive ingredients from various papers that discuss their Alzheimer's disease health benefits and applications. This process allows researchers to identify the most effective compounds for enhancing nutritional value and promoting wellness. Choose various compounds. Total 22 compounds were Selected out which only 21 compound were bound to protein. We retreat Canonical SMILES, Source, Molecular Formula, compound ID, compounds are

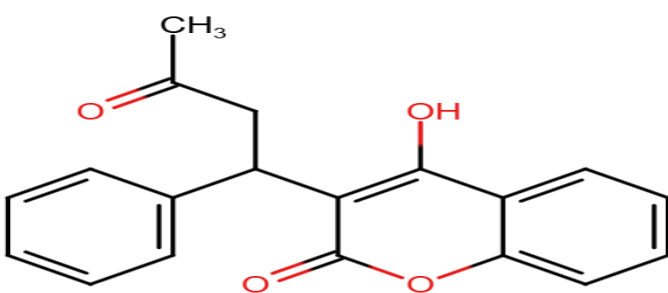
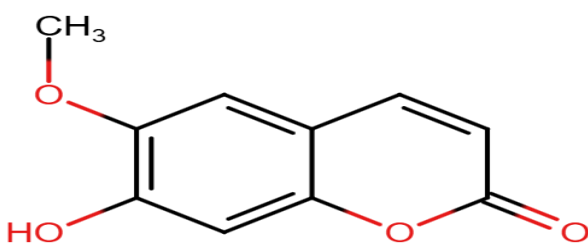
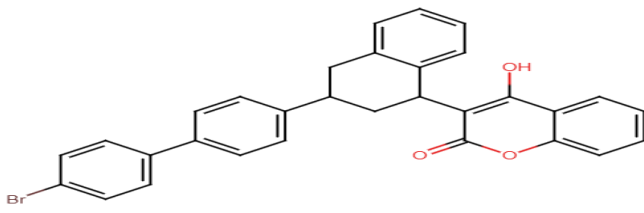
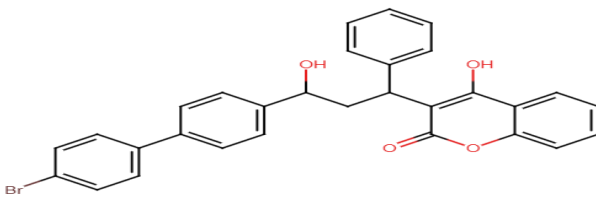
Table 3.1. Table of chenonicals smile of selected compounds.

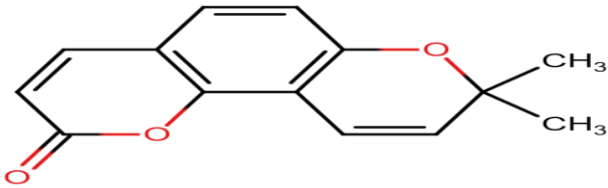
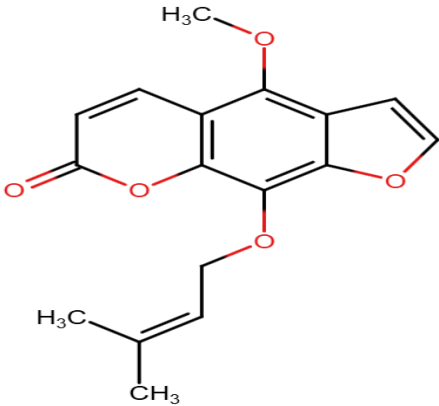
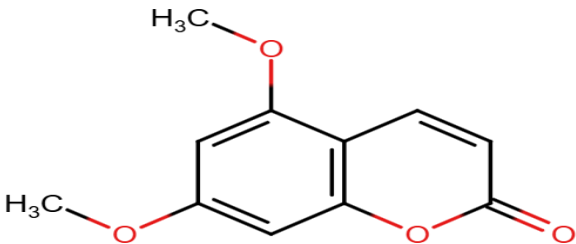
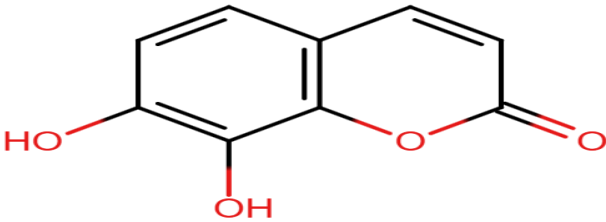
S.No	Name of Compounds	Smiles/ chenonicals
1	Difenacoum	<chem>C1C(CC2=CC=CC=C2C1C3=C(C4=CC=CC=C4OC3=O)O)C5=CC=C(C=C5)C6=CC=CC=C6</chem>
2	Umbelliferone	<chem>C1=CC(=CC2=C1C=CC(=O)O2)O</chem>
3	Esculetin	<chem>C1=CC(=O)OC2=CC(=C(C=C21)O)O</chem>
4	Esculin	<chem>C1=CC(=O)OC2=CC(=C(C=C21)O)[C@H]3[C@@H]([C@H]([C@H]([C@H](O3)CO)O)O)O</chem>
5	Fraxetin	<chem>COC1=C(C(=C2C=C1)C=CC(=O)O2)O</chem>
6	Dicoumerol	<chem>C1=CC=C2C(=C1)C(=C(C(=O)O2)CC3=C(C4=CC=CC=C4OC3=O)O)O</chem>
7	Psoralidin	<chem>CC(=CCC1=CC2=C(C=C1O)OC(=O)C3=C2OC4=C3C=CC(=C4)O)C</chem>
8	Auraptene	<chem>CC(=CCC/C(=C/COC1=CC2=C(C=C1)C=CC(=O)O2)/C)C</chem>
9	6-Hydroxy-4-methylcoumarin	<chem>CC1=CC(=O)OC2=C1C=C(C=C2)O</chem>
10	IMPERATORIN	<chem>CC(=CCOC1=C2C(=CC3=C1OC=C3)C=CC(=O)O2)C</chem>
11	Bergapten	<chem>COC1=C2C=CC(=O)OC2=CC3=C1C=CO3</chem>
12	Xanthotoxin k/a	<chem>COC1=C2C(=CC3=C1OC=C3)C=CC(=O)O2</chem>
13	Deltoin	<chem>C/C=C(C)C(=O)OC(C)(C)[C@H]1CC2=C(O1)C=C3C(=C2)C=CC(=O)O3</chem>
14	Osthole	<chem>CC(=CCC1=C(C=CC2=C1OC(=O)C=C2)OC)C</chem>
15	Warfarin	<chem>CC(=O)CC(C1=CC=CC=C1)C2=C(C3=CC=CC=C3OC2=O)O</chem>
16	Scopoletin	<chem>COC1=C(C=C2C(=C1)C=CC(=O)O2)O</chem>
17	Brodifacoum	<chem>C1C(CC2=CC=CC=C2C1C3=C(C4=CC=CC=C4OC3=O)O)C5=CC=C(C=C5)C6=CC=C(C=C6)Br</chem>
18	Bromadiolone	<chem>C1=CC=C(C=C1)C(CC(C2=CC=C(C=C2)C3=CC=C(C=C3)Br)O)C4=C(C5=CC=CC=C5OC4=O)O</chem>
19	Seselin	<chem>CC1(C=CC2=C(O1)C=CC3=C2OC(=O)C=C3)C</chem>
20	Phellopterin	<chem>CC(=CCOC1=C2C(=C(C3=C1OC(=O)C=C3)OC)C=CO2)C</chem>
21	Citropten /citropten	<chem>COC1=CC2=C(C=CC(=O)O2)C(=C1)OC</chem>
22	Daphnetin	<chem>C1=CC(=C(C2=C1C=CC(=O)O2)O)O</chem>

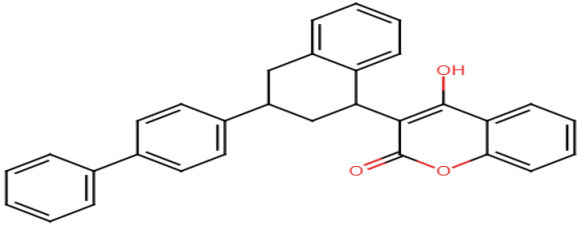
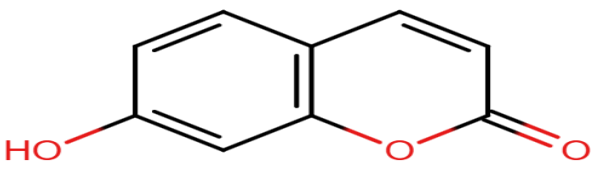
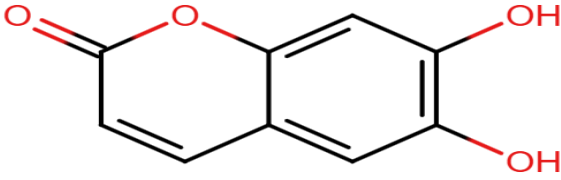
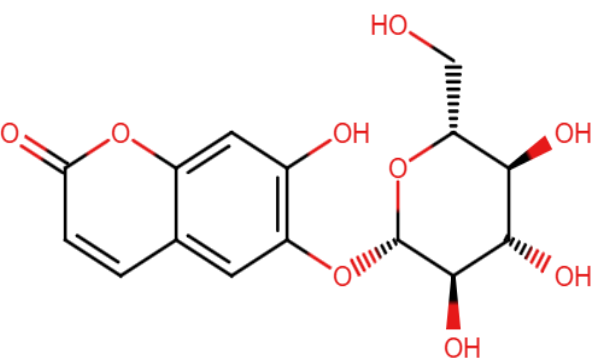
3.2. Molecular Structure

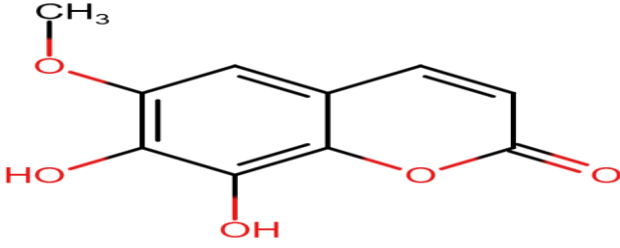
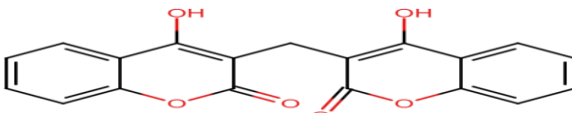
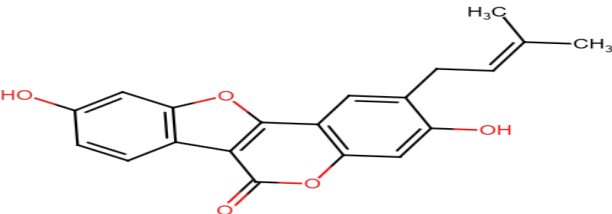
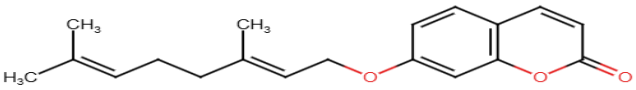
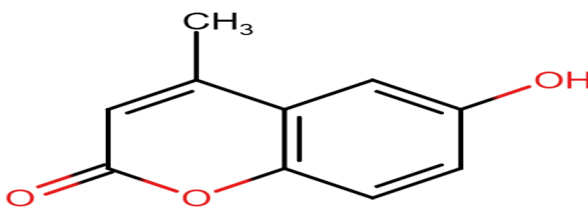
Table.3.1 Structure of Selected Molecular compounds

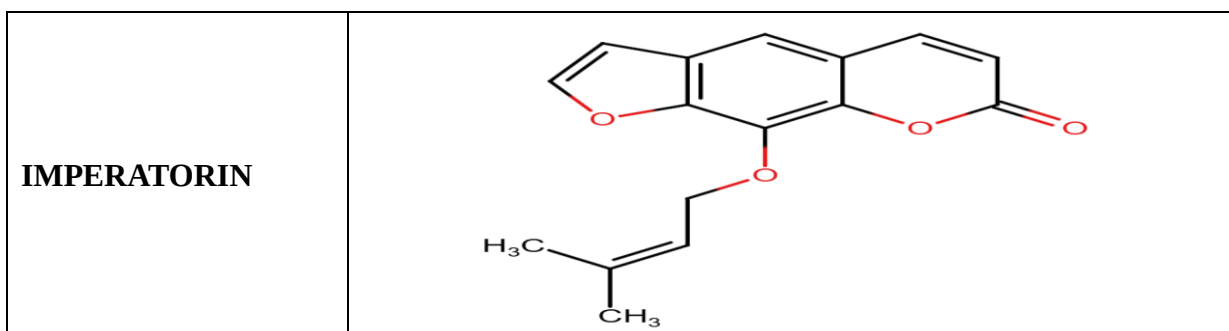
Compounds Name	Compound Structure
Bergapten	
Xanthotoxin k/a methoxsalen	
Deltoin	
Osthole	

Warfarin	 The chemical structure of Warfarin (4-[(3S)-3-(4-oxo-3-phenyl-1,3-dihydroisobenzofuran-2-yl)propyl]phenyl]phenylmethanone) is shown. It features a central coumarin ring system. At the 3-position of the coumarin, there is a propyl chain. The terminal carbon of this chain is part of a ketone group (C=O) attached to a phenyl ring. The 4-position of the coumarin is also attached to a phenyl ring.
Scopoletin	 The chemical structure of Scopoletin (6-methoxy-7-hydroxy-2H-chromene) is shown. It consists of a chromene core. A methoxy group (-OCH₃) is attached at the 6-position, and a hydroxyl group (-OH) is attached at the 7-position.
Brodifacoum	 The chemical structure of Brodifacoum is shown. It features a coumarin ring system. At the 3-position, there is a propyl chain. The terminal carbon of this chain is part of a ketone group (C=O) attached to a phenyl ring. The 4-position of the coumarin is also attached to a phenyl ring. The 6-position of the coumarin is attached to a phenyl ring, which is further substituted with a bromine atom (Br).
Bromadiolone	 The chemical structure of Bromadiolone is shown. It features a coumarin ring system. At the 3-position, there is a propyl chain. The terminal carbon of this chain is part of a ketone group (C=O) attached to a phenyl ring. The 4-position of the coumarin is also attached to a phenyl ring. The 6-position of the coumarin is attached to a phenyl ring, which is further substituted with a bromine atom (Br).

Seselin	
Phellopterin	
Citroptene /citropten	
Daphnetin	

Difenacoum	
Umbelliferone	
Esculetin	
Esculin	

Fraxetin	
Dicoumerol	
Psoralidin	
Auraptene	
6-Hydroxy-4-methylcoumarin	



3.3. Physicochemical Property

Distinction The primary goal of the ADMET analysis is to determine the compound's physiochemical properties. One important aspect of a medication is its solubility, which is represented as log S, the base-10 logarithm of a molecule. Solubility is expressed in moles/L. Better physical characteristics include hydrogen bonding, heavy atoms, molecular formula, HBA, and TPSA values. The physicochemical properties included both chemical and physical forms.

3.4. Drug likeness prediction

Every other chemical meets the requirements for "lead likeness." Although it relates to the physicochemical parameters that characterize a good lead, that is, a molecular entity that is druggable, this idea is similar to drug-likeness. By definition, leads also go through chemical derivatization, which is likely to increase their size and lipophilicity. Leads must therefore be smaller and less hydrophobic than molecules that resemble drugs. This extra filtering makes sense because, if the new approach is founded on a well-established scientific principle, it may be possible to obtain a lead that has not been empirically demonstrated to exhibit activity in any in vivo model. However, chemists frequently have to rule out obtaining a lead simply because it fits the chemical space of an existing lead when determining whether a molecule is suitable to begin the lead optimization process. **Daina et al.**^[13]

3.5. Predicting toxicity

Toxicological testing is necessary to lower the danger to humans and the environment. A key component of the green toxicology approach is minimizing the use of chemicals and animal experiments in toxicity assessment. The ProTox-III website has a number of benefits over current computational methods. The ProTox website includes both molecular and chemical target knowledge. The user can enter the substance's name or its SMILES (Simplified Molecular Input Line-Entry System) string to forecast possible toxicities linked to a chemical

structure. Additionally, the user has the option to use the chemical editor to help them sketch the chemical structure. Banerjee et al.^[4]

3.6. Selection of target Protein (receptor)

7MRM - The protein data bank (rcsb.org/structure/7MRM) provided the crystal structure of AMYLOID BETA (7MRM), which could be downloaded in PDB format. It is the goal of pharmacology while developing new medications to treat diseases. One of the Alzheimer disease receptor proteins is 7MRM.



Fig. 3.2: 3D structure of 7MRM protein.

3.7. Predicting ADME properties

A pharmaceutical molecule's pharmacokinetic profile plays a major role in determining its pharmacodynamic effects. SwissADME (<http://www.swissadme.ch/>) was used to study all twenty of the selected active compounds in order to evaluate these attributes. This brain-like device provided predispositions related to oral absorption, carcinogenic potential, and other characteristics related to human intestines. (Srivastava et al. 2022).^[57] The degree and duration of a drug's action are also described by pharmacodynamics. Binding off-target A drug may have toxic consequences, an adverse drug reaction, or unfavorable side effects if it binds to an unwanted target. It may also act on users' secondary biological targets or other pathways and receptors. When evaluating a drug's safety and effectiveness following oral

delivery, protein–drug interactions are crucial. Numerous databases that list drug-protein interactions have been created. **Singh S et al.**^[45]

3.8. Preparation of the receptor

Hydrogen atoms and Kollman charges were added to the 7MRM protein in order to prepare it for docking using AutoDock 4 (<https://autodock.scripps.edu/download-autodock4/>). The PDBQT format was used to save the file. Prior to being saved in the same manner, the ligand was similarly prepared by determining its root and modifying torsions. The docking region between the ligand and receptor was defined by a grid box. **Nisha et al.**^[34]

3.9. Molecular docking

Parameters like the Lamarckian technique and genetic algorithms were set up prior to the docking process beginning. Autogrid 4 and Autodock 4 (<https://autodock.scripps.edu/download-autodock4/>) were used for docking, resulting in GLG and DLG output files. The binding energy of the natural chemicals is included in the DLG file. **Srivastava et al.**^[43]

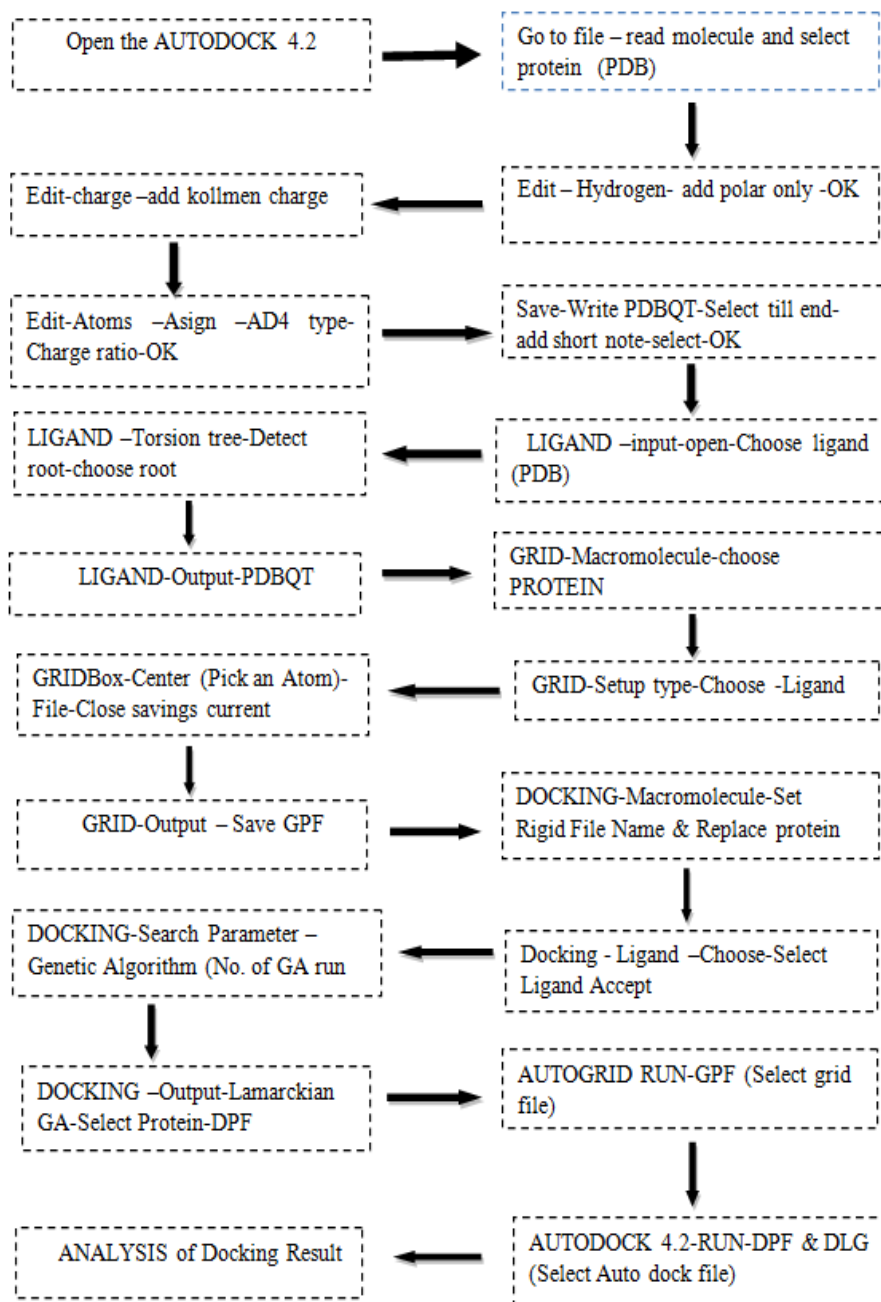


Fig. 3.4: Diagrammatic representation of the flow chart for the DOCKING PROCESS.

3.10. Predicting Protein Legend Interactions

The amino acids involved in the protein-ligand complex were examined using Plip Tool (<https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index>), which was also used to detect and tally several kinds of interactions, such as salt bridges, hydrogen bonds, and hydrophobic contacts. The PLIP program was used to upload the protein-ligand complex PDB file, and the analysis results were subsequently obtained. **Salentin et al.**^[44]

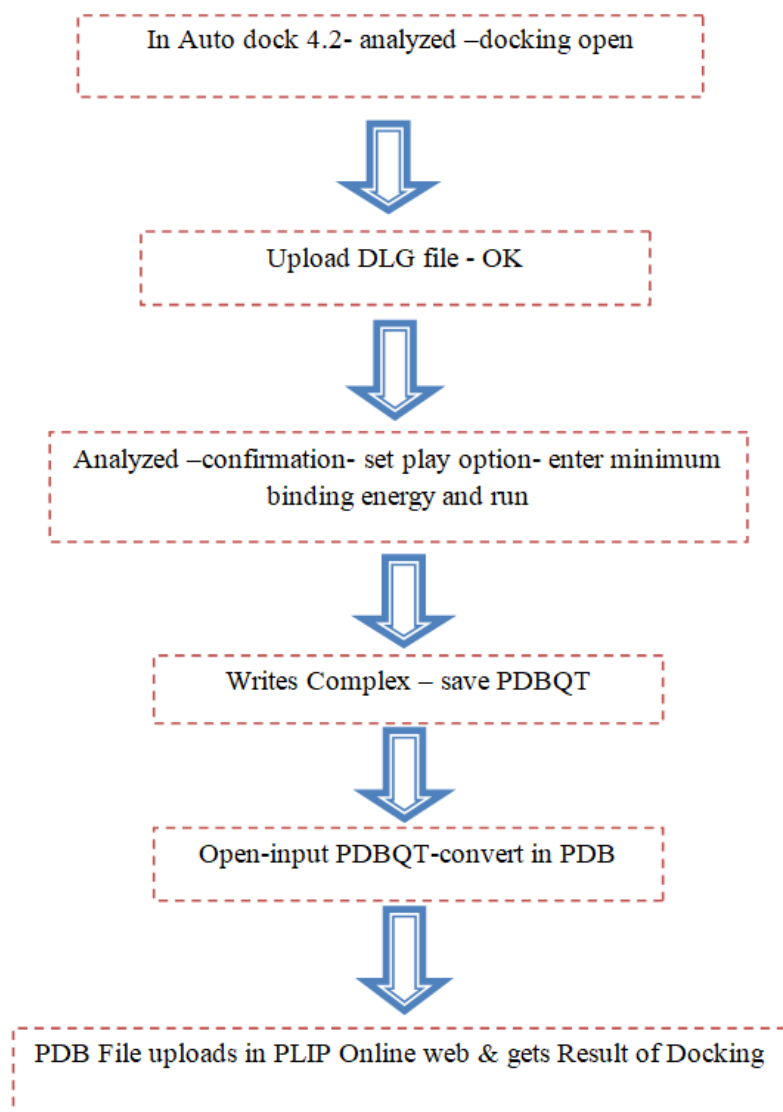


Fig. 3.5: A schematic representation of the flow chart for docking analysis.

CHAPTER-4

RESULT AND DISCUSSION

4.1. Obtained data of Selected Compound

Obtained the pubchem Id sources and Molecular Formula of the Selected Natural Compounds by use of pubchem website.

Table 4.1: Selected Compound sources and molecular formula.

S.No	Name of Compounds	Pubchem Id	Sources	Molecular Formula
1	Difenacoum	54676884	-diphenyl-1,2,3,4-hydronaphth-1-yl)-4-hydroxycou	C ₃₁ H ₂₄ O ₃
2	Umbelliferone	5281426	Carrot, celery, coriander, angelica, asafoetida	C ₉ H ₆ O ₃
3	Esculetin	5281416	Aloe vera plant	C ₉ H ₆ O ₄
4	Esculin	5281417	horse chestnut tree.	C ₁₅ H ₁₆ O ₉
5	Fraxetin	5273569	Fraxinus rhynchophylla, Datura stramonium	C ₁₀ H ₈ O ₅
6	Dicoumerol	54676038	Melilotus officinalis	C ₁₉ H ₁₂ O ₆
7	Psoralidin	5281806	Psoralea corylifolia	C ₂₀ H ₁₆ O ₅
8	Auraptene	1550607	Citrus aurantium and Aegle marmelos	C ₁₉ H ₂₂ O ₃
9	6-Hydroxy-4-methylcoumarin	75409	Glaucidium palmatum	C ₁₀ H ₈ O ₃
10	IMPERATORIN	10212	anise, bael fruit, and parsnip	C ₁₆ H ₁₄ O ₄
11	Bergapten	2355	Carrot family Apiaceae and the citrus family Rutaceae.	C ₁₂ H ₈ O ₄
12	Xanthotoxin k/a methoxsalen	4114	Ficus petiolaris	C ₁₂ H ₈ O ₄
13	Deltoin	906525	Balsamorhiza deltoidea	C ₁₉ H ₂₀ O ₅
14	Osthole	10228	Cnidium monnieri plant	C ₁₅ H ₁₆ O ₃
15	Warfarin	54678486	derived from coumarin	C ₁₉ H ₁₆ O ₄
16	Scopoletin	5280460	Redstem wormwood (Artemisia scoparia)	C ₁₀ H ₈ O ₄
17	Brodifacoum	54680676	Synthetic pesticide that comes from the 4-hydroxycoumarin group of compounds.	C ₃₁ H ₂₃ BrO ₃
18	Bromadiolone	54680085	meal bait, paraffinized pellet	C ₃₀ H ₂₃ BrO ₄
19	Seselin	68229	Sitrus plants like Shamouti orange, sour orange, sweet lime, and grapefruit.	C ₁₄ H ₁₂ O ₃
20	Phellopterin	98608	Roots of Angelica dahurica and Poncirus trifoliata	C ₁₇ H ₁₆ O ₅
21	Citroptene/citropten	2775	Citrus fruits like lemons, limes, and oranges.	C ₁₁ H ₁₆ O ₄
22	Daphnetin	5280569	Euphorbia semen and Matricaria chamomilla (chamomile).	C ₉ H ₆ O ₄

4.2. Physiochemical property of compounds

Discernment the Physiochemical property of the compound is main aim of the ADMET analysis. A key component of a drug like molecule is solubility which is denoted by log S, the base 10 logarithm of a molecule's Solubility Measured in mole/L. better physical properties contain heavy atoms, molecular formula, hydrogen bonding, HBA and TPSA Values. Both physical and chemical forms were present throughout the physicochemical qualities. The TPSA (Topological surface area) has the maximum Aesculin- 149.82 Å² and minimum value is Auraptene 39.44 Å², Osthole- 39.44 Å²

Table.4.2. Physiochemical property of the compound.

SR.No.	Name of Compounds	Formula	Molecular weight	No. Of Heavy atom	No.Of Rotable bonds	No. Of Hydrogen Bond acceptor	No.Of Hydrogen bonods Donar	TPSA (Topological surface Area)	Log P Value
1	Difenacoum	C ₃₁ H ₂₄ O ₃	444.52 g/mol	34	3	3	1	50.44 Å ²	6.27
2	Umbelliferone	C ₉ H ₆ O ₃	162.14 g/mol	12	0	3	1	50.44 Å ²	1.51
3	Esculetin	C ₉ H ₆ O ₄	178.14 g/mol	13	0	4	2	70.67 Å ²	1.12
4	Aesculin	C ₁₅ H ₁₆ O ₉	340.28 g/mol	24	3	9	5	149.82 Å ²	-0.56
5	Fraxetin	C ₁₀ H ₈ O ₅	208.17 g/mol	15	1	5	2	79.90 Å ²	1.11
6	Dicoumerol	C ₁₉ H ₁₂ O ₆	336.29 g/mol	25	2	6	2	100.88 Å ²	2.62
7	Psoralidin	C ₂₀ H ₁₆ O ₅	336.34 g/mol	25	2	5	2	83.81 Å ²	3.98
8	Auraptene	C ₁₉ H ₂₂ O ₃	298.38 g/mol	22	6	3	0	39.44 Å ²	4.51
9	6-Hydroxy-4-methylcoumarin	C ₁₀ H ₈ O ₃	176.17 g/mol	13	0	3	1	50.44 Å ²	1.82
10	Imperatorin	C ₁₆ H ₁₄ O ₄	270.28 g/mol	20	3	4	0	52.58 Å ²	3.31
11	Bergapten	C ₁₂ H ₈ O ₄	216.19 g/mol	13	1	4	0	52.58 Å ²	2.16
12	Xanthotoxin	C ₁₂ H ₈ O ₄	216.19 g/mol	13	1	4	0	52.58 Å ²	2.16
13	Deltoin	C ₁₉ H ₂₀ O ₅	328.36 g/mol	24	4	5	0	65.74 Å ²	3.46
14	Osthole	C ₁₅ H ₁₆ O ₃	244.29 g/mol	18	3	3	0	39.44 Å ²	3.34
15	Warfarin	C ₁₉ H ₁₆ O ₄	308.33 g/mol	23	4	4	1	67.51 Å ²	3.12
16	Scopoletin	C ₁₀ H ₈ O ₄	192.17 g/mol	14	1	4	1	59.67 Å ²	1.52
17	Brodifacoum	C ₃₁ H ₂₃ BrO ₃	523.42 g/mol	35	3	3	1	50.44 Å ²	6.77
18	Bromadiolone	C ₃₀ H ₂₃ BrO ₄	527.41 g/mol	35	6	4	2	70.67 Å ²	5.9
19	Seselin	C ₁₄ H ₁₂ O ₃	228.24 g/mol	17	0	3	0	39.44 Å ²	2.81
20	Phellopterin	C ₁₇ H ₁₆ O ₅	300.31 g/mol	22	4	5	0	61.81 Å ²	3.36
21	Citroptene / citropten	C ₁₁ H ₁₀ O ₄	206.19 g/mol	15	2	4	0	48.67 Å ²	1.92
22	Daphnetin	C ₉ H ₆ O ₄	178.14 g/mol	13	0	4	2	70.67 Å ²	1.08

4.3. Pharmacokinetic Properties

Pharmacokinetics properties including the whole ADME (Absorption, Distribution, Metabolism, and Excretion). Absorbtion is the procedure in which drug reached in the circulation and cell/tissue. It included the blood brain barrier, gastrointestinal absorption. According to the finding computational data Difenacoum, Aesculin, Brodifecoum, Bromadiolone have low potency GI Absorption, and Difenacoum, Brodifecoum, Bromadiolone these show Lipinski violation. The drug molecule is not possessing the blood brain barrier thats is BBB due to their lipophilic nature.log kp is the show skin permeation. The compounds have the difference value.

Table 4.3: Pharmacokinetics properties of ligands.

Sr. No.	Compound NAME	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19	CYP2D6	CYP3A4	Log Kp	Lipinski
1	Difenacoum	low	no	No	no	no	no	no	-3.47 cm/s	Yes; 1 violation: MLOGP>4.15
2	Umbelliferone	High	Yes	No	Yes	No	No	No	-6.17 cm/s	Yes; 0 violation
3	Esculetin	High	No	NO	Yes	No	No	No	-6.52 cm/s	Yes; 0 violation
4	Aesculin	Low	No	No	No	No	No	No	-8.81 cm/s	Yes; 0 violation
5	Fraxetin	High	No	No	No	No	No	No	-6.74 cm/s	Yes; 0 violation
6	Dicoumerol	High	NO	NO	Yes	No	NO	NO	-6.88 cm/s	Yes; 0 violation
7	Psoralidin	High	No	No	Yes	Yes	No	No	-5.02 cm/s	Yes; 0 violation
8	Auraptene	High	Yes	No	Yes	Yes	No	No	-4.50 cm/s	Yes; 0 violation
9	6-Hydroxy-4-methylcoumarin	High	Yes	No	Yes	NO	No	No	-6.03 cm/s	Yes; 0 violation
10	Imperatorin	High	Yes	No	YES	Yes	No	No	-5.46 cm/s	Yes; 0 violation
11	Bergapten	High	Yes	No	Yes	NO	No	NO	-6.25 cm/s	Yes; 0 violation
12	Xanthotoxin	High	Yes	No	Yes	No	No	No	-6.20 cm/s	Yes; 0 violation
13	Deltoidin	High	Yes	No	Yes	Yes	No	Yes	-5.68 cm/s	Yes; 0 violation
14	Osthole	High	Yes	No	Yes	Yes	NO	No	-5.09 cm/s	Yes; 0 violation
15	Warfarin	High	Yes	No	No	Yes	No	No	-6.26 cm/s	Yes; 0 violation
16	Scopoletin	High	Yes	No	Yes	No	No	No	-6.39 cm/s	Yes; 0 violation
17	Brodifacoum	Low	No	No	Yes	No	No	NO	-3.46 cm/s	No; 2 violations: MW>500, MLOGP>4.15
18	Bromadiolone	Low	No	No	No	No	No	No	-5.21 cm/s	No; 2 violations: MW>500, MLOGP>4.15
19	Seselin	High	Yes	No	Yes	Yes	No	No	-5.68 cm/s	Yes; 0 violation
20	Phellopterin	High	Yes	No	Yes	Yes	No	No	-5.47 cm/s	Yes; 0 violation
21	Citroptene /citropten	High	Yes	No	Yes	No	NO	NO	-6.24 cm/s	Yes; 0 violation
22	Daphnetin	High	NO	No	Yes	NO	No	No	-6.53 cm/s	Yes; 0 violation

4.4. Drug likeness

Table 4.4: Drug likeness model score char.

Sr.No.	Name of Compounds	Drug-likeness model score
1	Difenacoum	0.80
2	Umbelliferone	0.65
3	Esculetin	1.22
4	Aesculin	0.02
5	Fraxetin	0.96
6	Dicoumerol	0.02
7	Psoralidin	0.59
8	Auraptene	0.3
9	6-Hydroxy-4-methylcoumarin	0.25
10	IMPERATORIN	0.82
11	Bergapten	0.65
12	Xanthotoxin	1.16
13	Deltoidin	1.09
14	Osthole	0.48
15	Warfarin	0.59
16	Scopoletin	1.23
17	Brodifacoum	0.78
18	Bromadiolone	0.81
19	Seselin	-1.34
20	Phellopterin	-0.52
21	Citroptene /citropten	1.27
22	Daphnetin	1.09

Drug-likeness is used in drug design to evaluate how "drug-like" a compound is, i.e., how suitable it is to become an effective, safe, and bioavailable drug. Drug resemblance prediction using Molsoft tool. Checked drug likeness properties a total of 22 compounds. Maximum drug likeness value is Xanthotoxin (1.16) the lowest likeness property of seselin (-1.34).

4.5. Toxicity Prediction

One consideration when selecting a possible molecule therapy option its lack of poisoning. The current study predicted the toxicological endpoints of the fifteen phytoconstituents, including immunotoxicity, carcinogenicity, cytotoxicity, mutagenicity, and organ toxicity (hepatotoxicity). Cytotoxicity, immunotoxicity, hepatotoxicity, and binary features (active or inactive for certain cell types) were used to assess their qualitative quality. The quantitative assessment was based on LD50 (lethal dosage) values. ProTox III was used to calculate a variety of toxicity metrics, including cytotoxicity, LD50 values,. The results show that none of the phytoconstituents are hepatotoxic. The range of the mean lethal dosage (LD50) was shown to be between 159 and 5000 mg/kg.

Table 4.5. Toxicity Prediction chart.

Sr No	Compound name	LD 50 Value	Predicted Toxicity Class	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	BBB-barrier
1	Difenacoum	1mg/kg	1	Active	Inactive	Inactive	Inactive	Active
2	Umbelliferone	10000mg/k	6	Active	Inactive	Inactive	Inactive	Inactive
3	Esculetin	945mg/kg	4	Active	Inactive	Inactive	Inactive	Active
4	Aesculin	4000mg/kg	5	Inactive	Active	Inactive	Inactive	Active
5	Fraxetin	3800mg/kg	5	Active	Active	Inactive	Inactive	Inactive
6	Dicoumerol	233mg/kg	3	Inactive	Inactive	Inactive	Inactive	Active
7	Psoralidin	1190mg/k	4	Inactive	Active	Inactive	Inactive	Inactive
8	Auraptene	3200mg/kg	5	Inactive	Inactive	Inactive	Inactive	Active
9	6-Hydroxy-4-	2850mg/kg	5	Active	Inactive	Inactive	Inactive	Inactive
10	IMPERATORIN	480mg/kg	4	Inactive	Active	Active	Inactive	Active
11	Bergapten	8100mg/kg	6	Active	Inactive	Active	Inactive	Active
12	Xanthotoxin	423mg/kg	4	Active	Inactive	Active	Inactive	Active
13	Deltoin	832mg/kg	4	Inactive	Inactive	Inactive	Inactive	Active
14	Osthole	2905mg/kg	5	Inactive	Inactive	Inactive	Inactive	Active
15	Warfarin	2mg/kg	1	Inactive	Inactive	Inactive	Inactive	Active
16	Scopoletin	3800mg/kg	5	Active	Active	Inactive	Inactive	Active
17	Brodifacoum	1mg/kg	1	Active	Inactive	Inactive	Inactive	Active
18	Bromadiolone	1mg/kg	1	Inactive	Inactive	Active	Inactive	Active
19	Seselin	3850mg/kg	5	Active	Active	Inactive	Inactive	Active
20	Phellopterin	1100mg/kg	4	Inactive	Active	Active	Inactive	Active
21	Citroptene/citropten	3200mg/kg	5	Active	Inactive	Inactive	Inactive	Active
22	Daphnetin	5370mg/kg	6	Active	Inactive	Inactive	Inactive	Active

4.6. Molecular docking

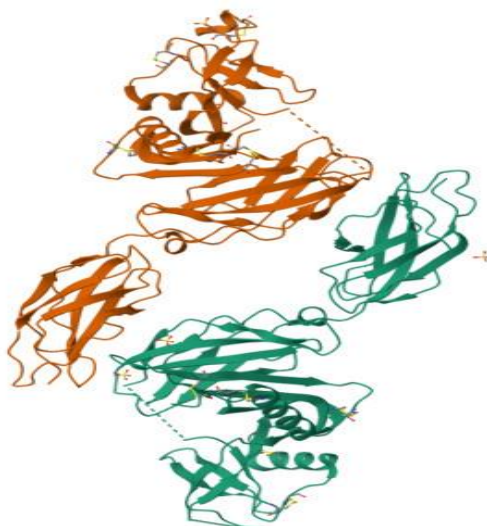
Out of the 22 flavonoid compounds, 20 have extra activities and bind to the PYCARD (7mm) protein. It is crucial to remember that logical drug design relies on Lipinski's rule of five. It has been proposed that a molecule will probably have poor absorption or low permeability if one of the five restrictions is broken. Flavonoids, alkaloids, terpenoids, and other chemicals exhibit drug-like molecular characteristics and possess six NHBDs (> 5) in their structure. These substances are categorized according to Lipinski's five rules for availability. The goal of the study was to predict the degree to which fifteen specific phytoconstituents will bind to the target protein.

Table 4.6. Binding property of legends.

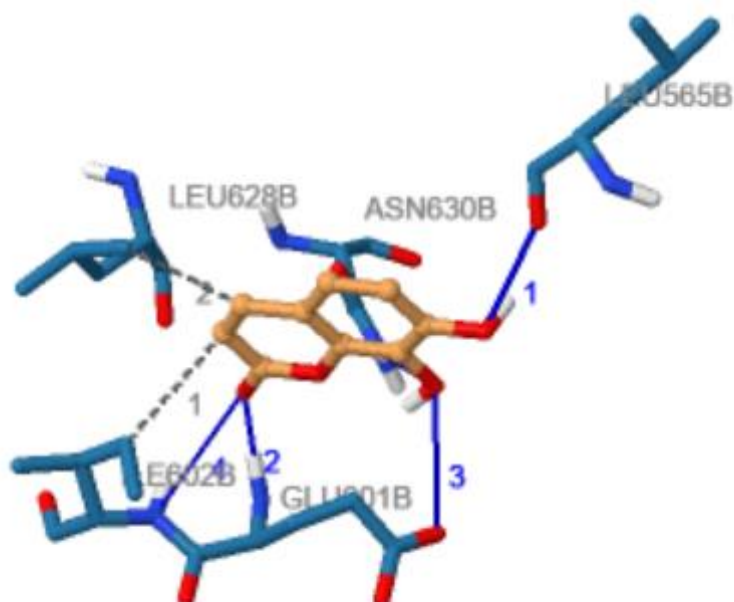
Sr. No.	Compound Name	RSMD Value (Binding energy)
1	Difenacoum	-6.69
2	Umbelliferone	-5.47
3	Esculetin	-10.03
4	Aesculin	-2.38
5	Fraxetin	-5.93
6	Dicoumerol	-7.05
7	Psoralidin	-7.24
8	Auraptene	-7.04
9	6-Hydroxy-4-methylcoumarin	-5.23
10	IMPERATORIN	-5.65
11	Bergapten	-5.62
12	Xanthotoxin	-6.06
13	Osthole	-5.58
14	Warfarin	-7.04
15	Scopoletin	-5.77
16	Bromadiolone	-5.36
17	Seselin	-6.32
18	Phellopterin	-5.44
19	Citropten /citropten	-5.4
20	Daphnetin	-5.32

4.7. Molecular docking Evaluation by PLIP Tool

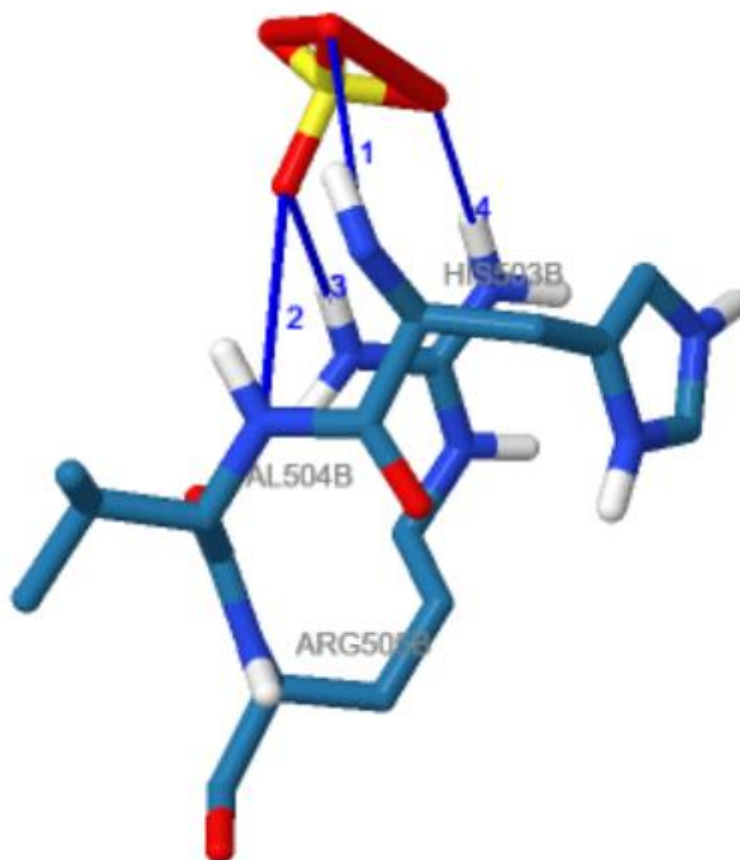
7MRM is the transcription factor these are augmentation in the Alzheimer disease. In this work we present the interaction between 7MRM and natural compounds. Over all 22 compounds are included in this two are not bind with the target remaining 20 compounds are binds with the protein. And shoe interaction.



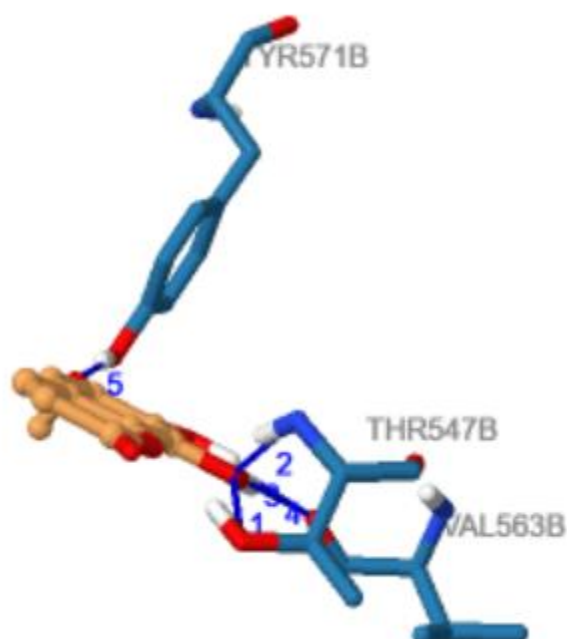
Structure of 7MRM Protein from RCSB software



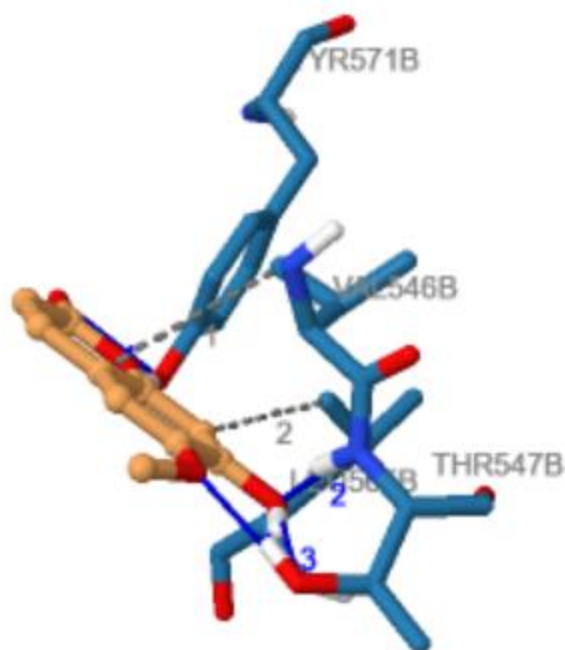
Daphnetin's binding mode represented using 7MRM protein from PLIP Tool



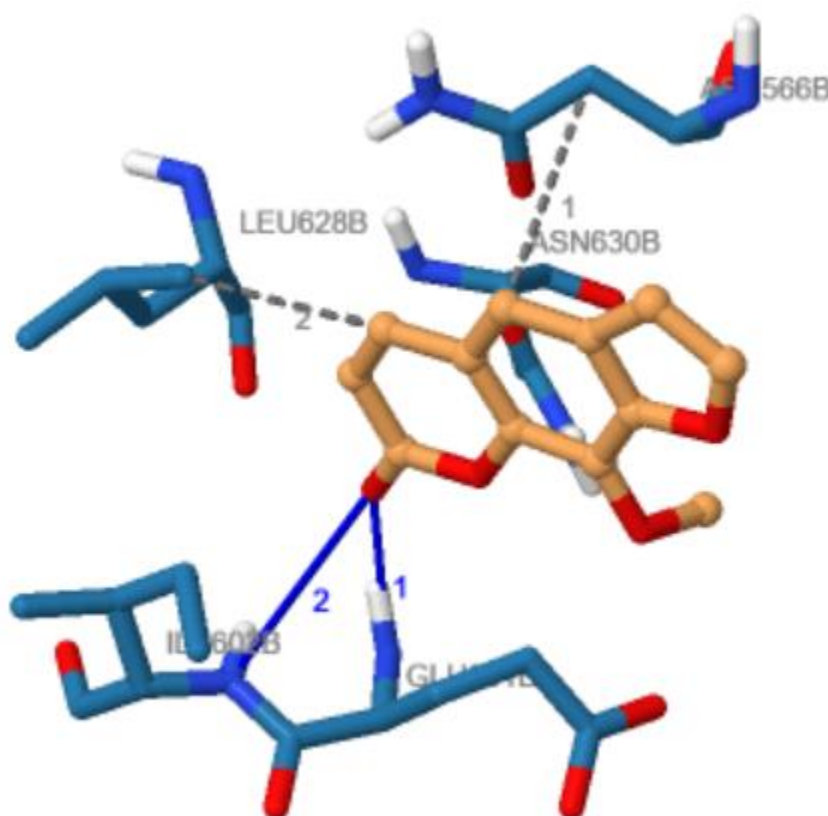
Imperatorin binding mode represented using 7MRM protein from PLIP Tool



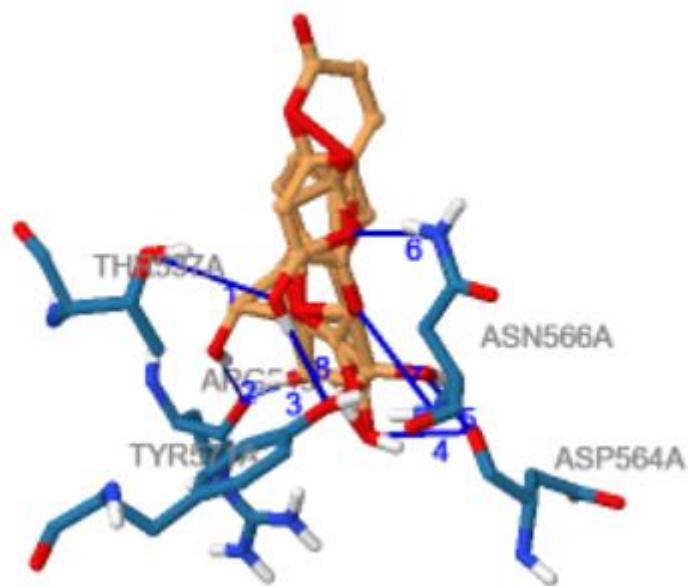
Fraxetin binding mode represented using 7MRM protein from PLIP Tool



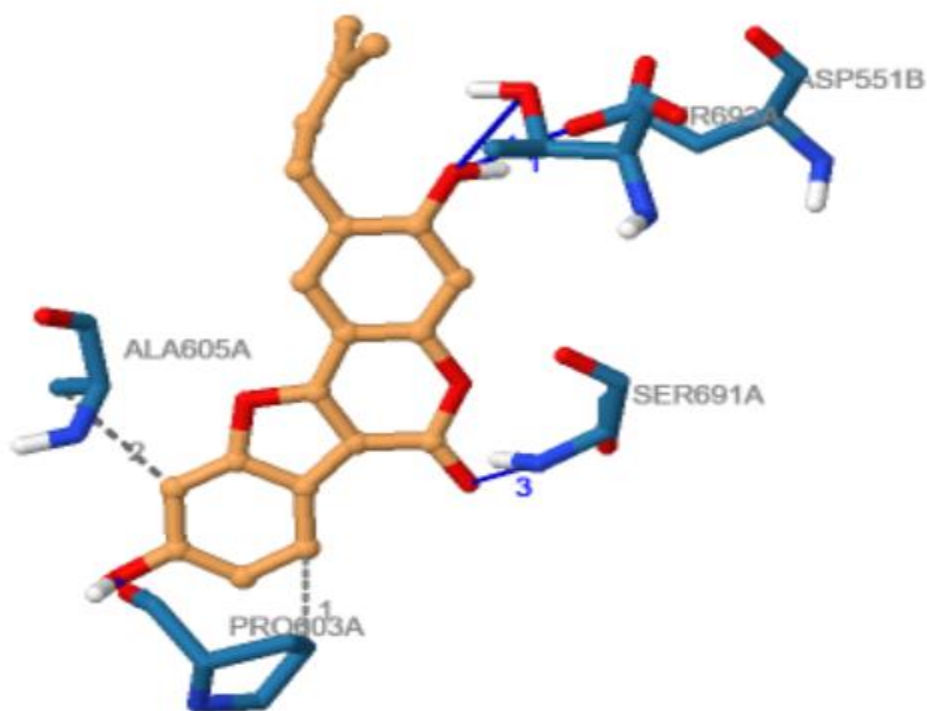
Scopolatin binding mode represented using 7MRM protein from PLIP Tool



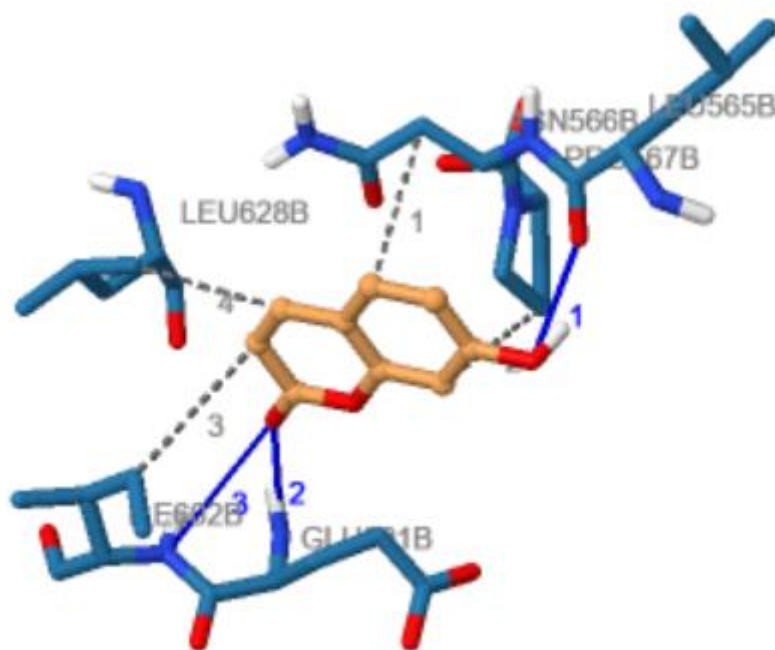
Methoxsalen binding mode represented using 7MRM protein from PLIP Tool



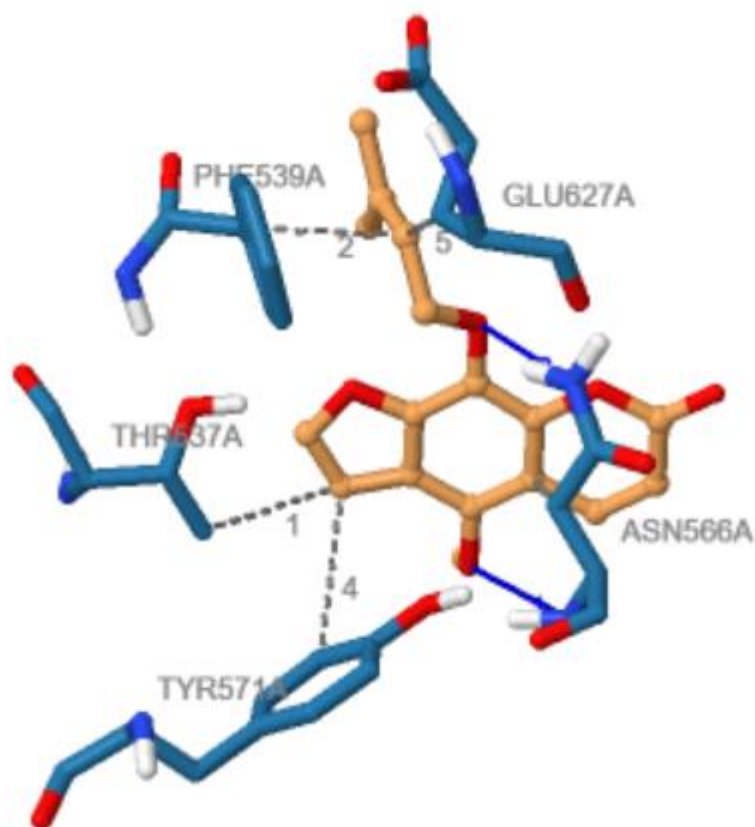
Esculin binding mode represented using 7MRM protein from PLIP Tool.



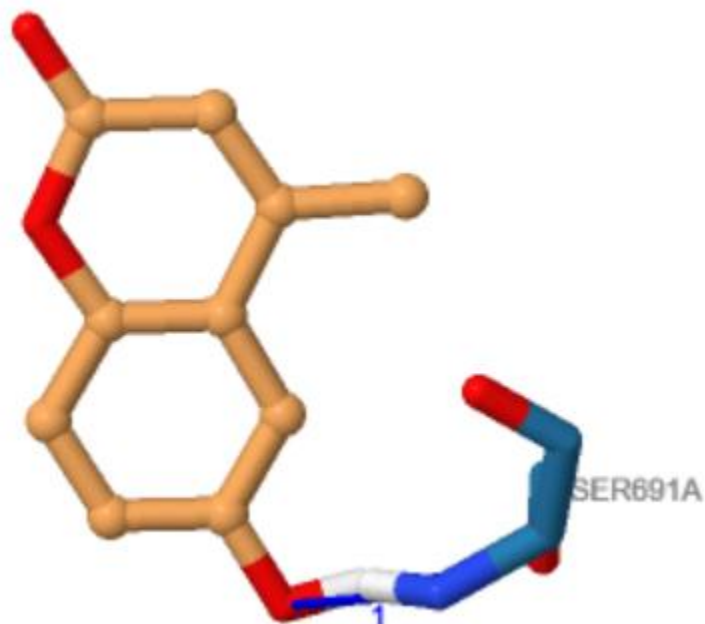
Psolaridin binding mode represented using 7MRM protein from PLIP Tool



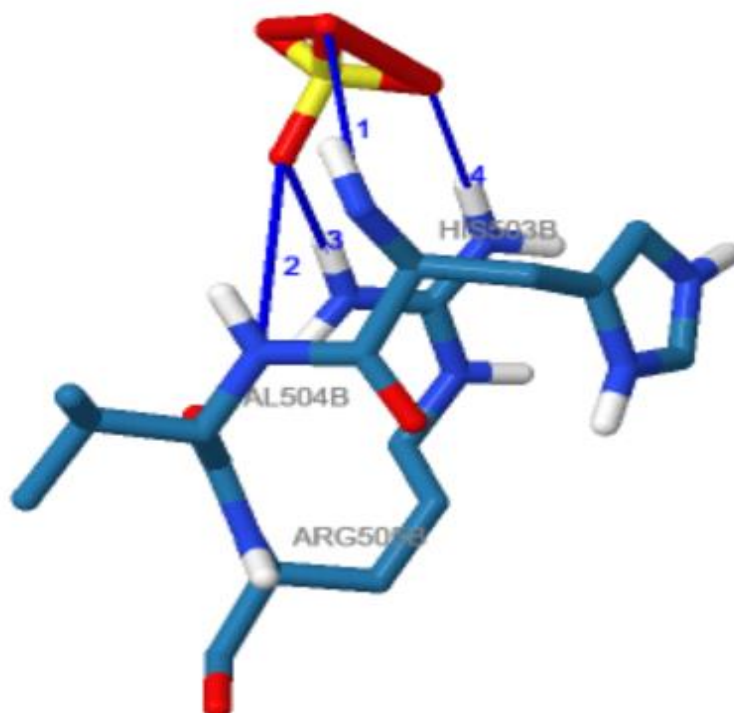
Umbelliferone binding mode represented using 7MRM protein from PLIP Tool



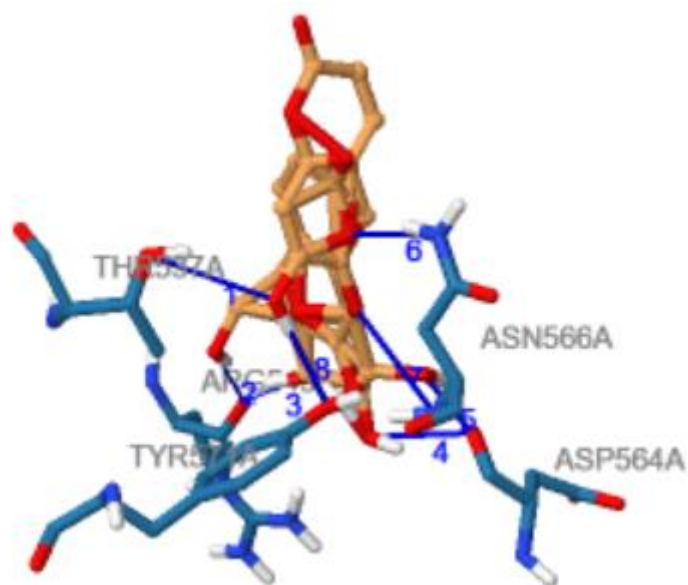
Phelloptrin binding mode represented using 7MRM protein from PLIP Tool



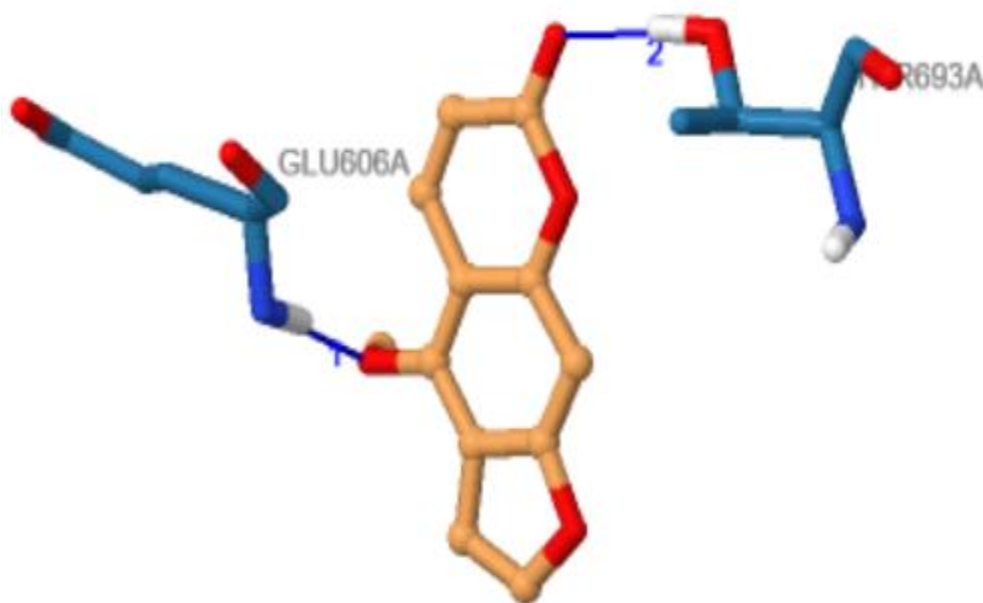
6-Hydroxy-4- Methoxy coumarin binding mode represented using 7MRM protein from PLIP Tool



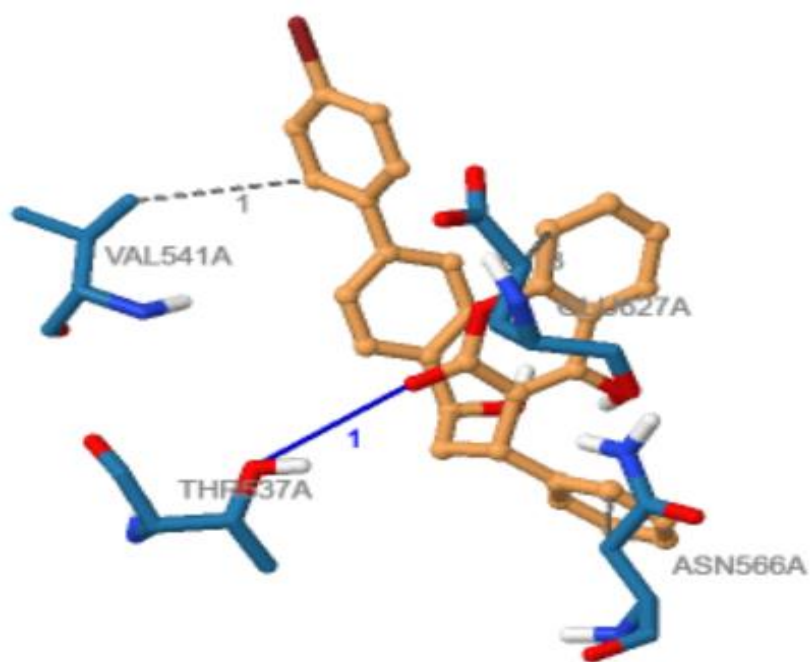
Auraptene binding mode represented using 7MRM protein from PLIP Tool



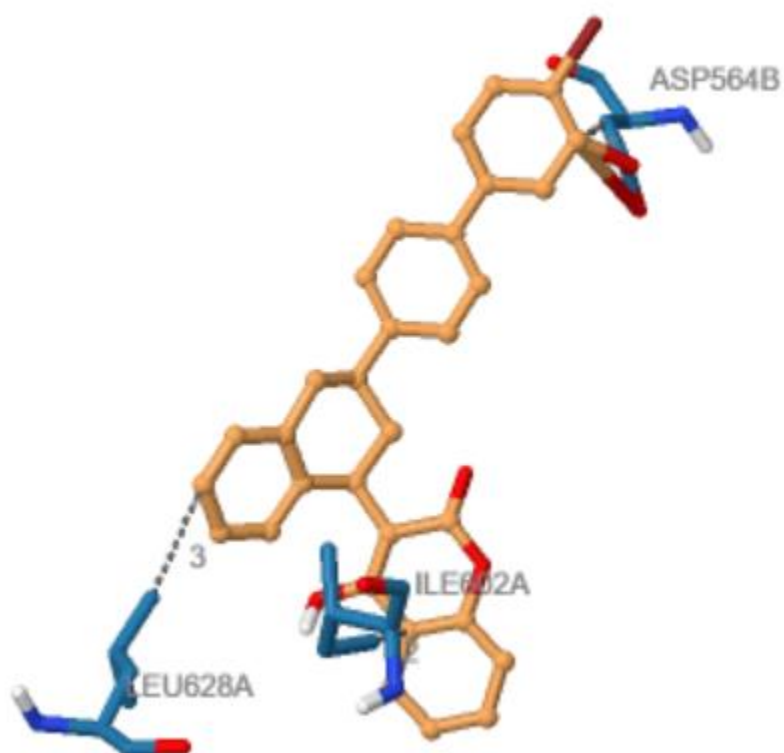
Esculetin binding mode represented using 7MRM protein from PLIP Tool



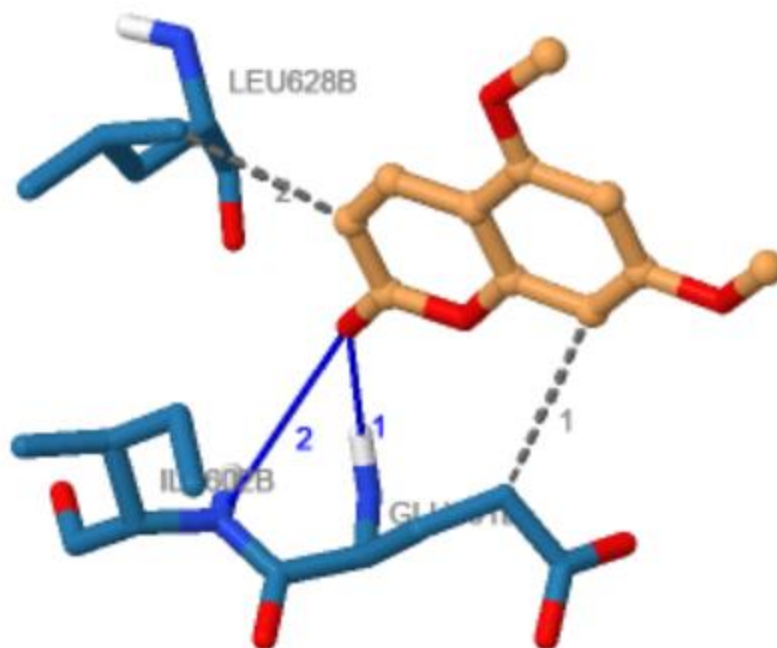
Bergepten binding mode represented using 7MRM protein from PLIP Tool



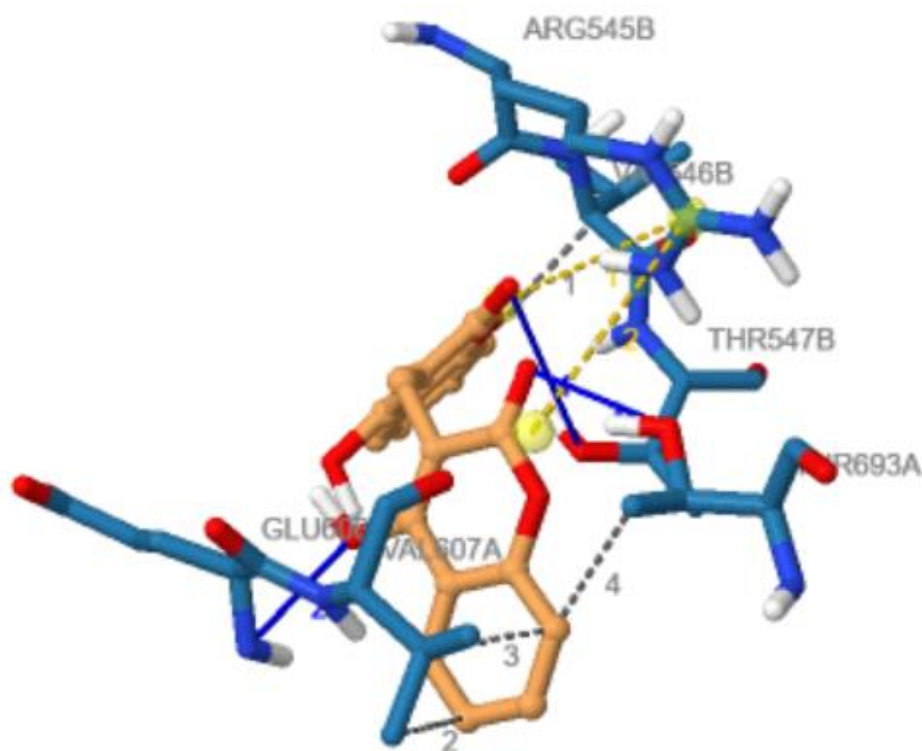
Bromodiolone binding mode represented using 7MRM protein from PLIP Tool



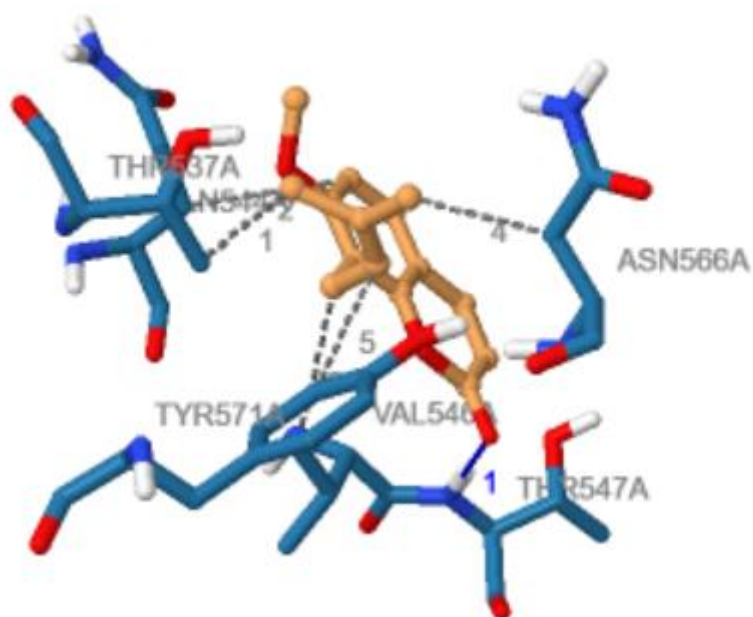
Brodifacoum binding mode represented using 7MRM protein from PLIP Tool



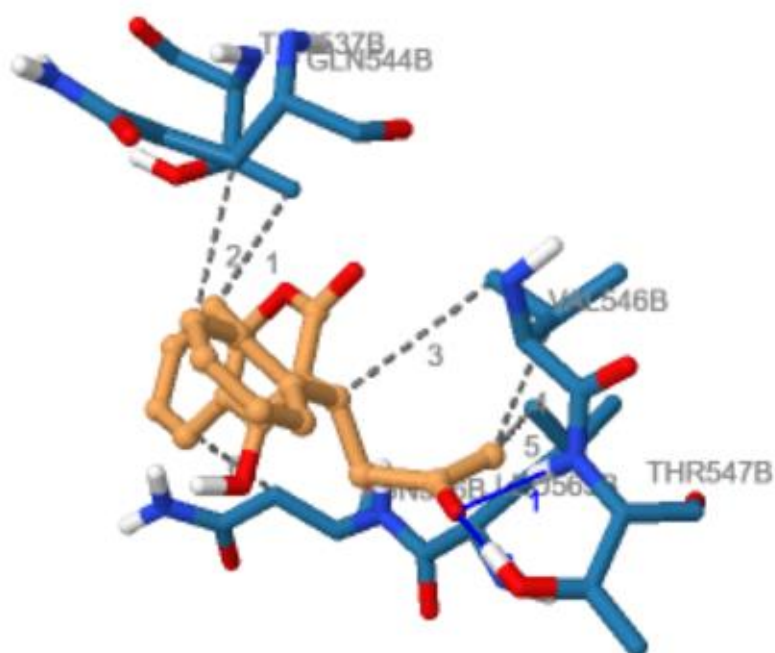
Citropten binding mode represented using 7MRM protein from PLIP Tool



Dicoumerol binding mode represented using 7MRM protein from PLIP Tool



Osthale binding mode represented using 7MRM protein from PLIP Tool



Warferin binding mode represented using 7MRM protein from PLIP Tool

Fig. 4.1: Representing PLIP binding structure of legends and Protein.

Table 4.7: Molecular Docking Value of Compounds against 7MRM.

Sr.	Compound	HYDROPHOBIC INTRACTION AND OTHER INTRACTION	HYDROGEN BONDS
1	Difenacoum	ALA-535B, THR-537B, GLN-544B, ASN-566B, TYR-571B, GLV-601B, ILE-602B, LEV-626B	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B, THR-646B, THR-647B, HIS-503B, VAL-504B, ARG-505B,
2	Umbelliferone	ASN-566B, PRO-567B, ILE-602B, LEV-628B	LYS-1040A, ASN-1106A, HIS-1110A, THR-646B, THR-647B, HIS-503B,
3	Esculetin		LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B, HIS-503B, VAL-504B, ARG-505B
4	Aesculin	HIS-503B, VAL-504B, ARG-505B, ARG-505B, THR-537A, ARG-545A, ASP-564A,	LYS-1040A, ASN-1106A, HIS-1110, THR-646B, THR-647B,
5	Fraxetin	TYR-571B, VAL-563B	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B, THR-646B, THR-647B, HIS-503B, VAL-563B
6	Dicoumerol	VAL-546B, VAL-607A, THR-693A	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-68B, THR-646B, VAL-504B,
7	Psoralidin	PRO-603A, ALA-605A	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B, THR-646B, THR-647B, HIS-503B
8	Auraptene	GLU-686B, VAL-1129, LYS-1134B, CEU-1135B, CEU-1136B,	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B
9	6-Hydroxy-4-methylcoumarin	NO	LYS-1040A, ASN-1106, HIS-1110, ARG-641B, TRP-648B
10	IMPERATORIN	THR-537A, VAL-504B	LYS-1140A, ASN-1106A, HIS-1110A
11	Bergapten	NO	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B, GLV-606A, THR-693A
12	Xanthotoxin/ME THOXSALEN	HIS-503B, VAL-504B, ARG-505B, ASN-566B, LEV-628B,	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, ARG-641B, TRP-648B
13	Osthole	THR-537A, GLN-544A, VAL-546A, ASN-566A, TYR-571A	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641A,
14	Warfarin	THR-547B, GLN-544B, AL-546B, LEV-556B, ASN-566B	LYS-1040A, ASN-1106A, HIS-1110A, ARG-614VB
15	Scopoletin	GLN-544A	LYS-1140A, ASN-1106A, HIS-1110A
16	Bromadiolone	VAL-540A, ASN-566A, GLU-627A	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B
17	Seselin	VAL-607A, THR-693A, VAL-607A	LYS-1040A, ASN-1106A, HIS-1110, ARG-614B, TRP-648B
18	Phellopterin	THR-537A, PHE-539A, ASN-566A, TYR-571A, GNV-627A	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B
19	Citropten /citropten	GLU-601B, 602B-ILE, LEU-628B	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, TRP-648B
20	Daphnetin	ILE-602B, LEU-628B	LYS-1040A, ASN-1106A, HIS-1110A, ARG-641B, ARG-648B, TRP-648B,

Amino acids are primarily involved in the bonding and docking of ligands with 7mrm and hydrogen bonds. Such as - HIS-503B, VAL-504B, ARG-505B, ARG-505B, THR- 537A, ARG-545A, ASP-564A, some ligand are not show the hydrophobic intraction.

4.8. CONCLUSION

The physical, chemical, bioactive, and molecular docking characteristics of the ligand that the protein 7mrm, which is involved in Alzheimer's disease, targets were assessed and computed. We employed readily available medications, natural plant sources, and comparison controls to create a new inhibitor of the 7mrm protein. They score higher and have better protein binding. The plant-based flavonoids that we utilize are difenacoum, umbelliferone, and psoralidin; the alkaloids are dicoumerol, and all of the chosen ligands are plant-based. molecular examination and associated physicochemical properties. because a well-known antagonist of suggested leads has the same binding affinity as the recommended leads. It guarantees that potent inhibitors will be produced by the suggested leads. The toxicity profile, pharmacokinetics, and pharmacological show of a single synthesized compound that shows higher values and lower toxicity. In this found the log p property is changes scopoletin, cetropoten, daphnetin, asculin, 6 hydroxy-4-methylcoumarin, Bergepten, xanthotoxin,

scopolatin, Warferin show more negativity and daphnetin, dicoumarol, psoralidin, auraptine, bergeptine, oathole, brodifacoum lower affinity. These legands show various docking binding affinity- Auraptine(-7.04), Bergepten(-5.62), Bromodiolone(-5.36), Citropen(-5.40), Daphnetin(-5.32), Dicoumerol(-7.05), Difenacoum(-6.69), Esculetin(-10.03), Esculin(-2.38), Fraxetin(-5.93), methoxsalen(-6.06), osthole(-5.58), Psoralidin(-7.24), Scopoletin(-5.77), Seselin (-6.32), Umbelliferone(-5.47), Warferin (-7.04), Impratonin(5.65). The targeted drug has a lower binding energy than a natural molecule. Two ligands (Deltoin and brodifacoum) do not properly bind with proteins, while 22 of the 20 natural ligands bind with the targeted protein. However, Additional computer research is required to validate the findings presented in this article the molecule's toxicity concerns, bioactivity, pharmacokinetics, drug-likeness, and drug scores. These factors must be thoroughly assessed to guarantee the medication's effectiveness and safety before it can progress to clinical trials. Researchers are optimistic that optimizing these parameters will enhance the therapeutic potential of the targeted drug.

4.9. FUTURE PROSPECTIVE

To effectively harness the promise for treatment of medicinal plants in the context of Alzheimer, future research should concentrate on the following areas:

1. The separation and elucidation of bioactive compounds' structures.
2. Mechanistic studies to determine their mechanism of action against Alzheimer.
3. Research that uses natural products in conjunction with currently prescribed drugs in a synergistic way to boost effectiveness and reduce toxicity.
4. Creating standardized plant-based formulations that adhere to good manufacturing principles (GMP) and are backed by clinical data.
5. Identify iconic medicinal herbs that are effective against Alzheimer's and document traditional knowledge through community-managed dynastic research.
6. For the treatment of Alzheimer, a thorough, multidisciplinary approach may offer safer, more affordable, and more accessible medical choices, particularly in areas with low resources.

REFERENCES

1. Amin, Adnan, Muhammad Hanif, Khizar Abbas, Muhammad Ramzan, Abdur Rasheed, Ali Zaman, and Luc Pieters. "Studies on effects of umbelliferon derivatives against periodontal bacteria; antibiofilm, inhibition of quorum sensing and molecular docking analysis." *Microbial pathogenesis*, 2020; 144: 104184.

2. Agrawal, Shivangi, Ekta Pathak, and Rajeev Mishra. "Esculin as a Novel Inhibitor of CCR1: Insights into Its Potential Role in Modulating Immune Responses, (2024).
3. Altschul, Stephen F., John C. Wootton, E. Michael Gertz, Richa Agarwala, Aleksandr Morgulis, Alejandro A. Schäffer, and Yi-Kuo Yu. "Protein database searches using compositionally adjusted substitution matrices." *The FEBS journal* 272, 2005; 20: 5101-5109.
4. Banerjee, Priyanka, Andreas O. Eckert, Anna K. Schrey, and Robert Preissner. "ProTox-II: a webserver for the prediction of toxicity of chemicals." *Nucleic acids research*, 2018; 46: W1 W257-W263.
5. Bitew, Mamaru, Tegene Desalegn, Taye B. Demissie, Anteneh Belayneh, Milkyas Endale, and Rajalakshmanan Eswaramoorthy. "Pharmacokinetics and drug-likeness of antidiabetic flavonoids: Molecular docking and DFT study." *Plos one*, 2021; 16(12): e0260853.
6. Borul SB, Patil SS. Study of Drug Likeness Properties of Substituted Indazoles. *International Journal of Creative Research Thoughts (IJCRT).*, 2022; 10(2): 58–66.
7. Bunch, T. Jared, Heidi T. May, Tami L. Bair, Brian G. Crandall, Michael J. Cutler, John D. Day, Victoria Jacobs et al. "Atrial fibrillation patients treated with long-term warfarin anticoagulation have higher rates of all dementia types compared with patients receiving long-term warfarin for other indications." *Journal of the American Heart Association*, 2016; 5(7): e003932.
8. Breijyeh, Zeinab, and Rafik Karaman. "Comprehensive review on Alzheimer's disease: causes and treatment." *Molecules* 25, 2020; 24: 5789.
9. Chen, Chen-Peng, Chan-Cheng Chen, Chia-Wen Huang, and Yen-Ching Chang. "Evaluating molecular properties involved in transport of small molecules in stratum corneum: A quantitative structure-activity relationship for skin permeability." *Molecules* 23, 2018; 4: 911.
10. Choong, Eva, Maria Dobrin, Pierre-Alain Carrupt, and Chin B. Eap. "The permeability P-glycoprotein: a focus on enantioselectivity and brain distribution." *Expert opinion on drug metabolism & toxicology*, 2010; 6(8): 953-965.
11. Chiu, Ya-Jen, Te-Hsien Lin, Chiung-Mei Chen, Chih-Hsin Lin, Yu-Shan Teng, Chung-Yin Lin, Ying-Chieh Sun et al. "Novel Synthetic Coumarin-Chalcone Derivative(E)-3-(3-(4-(Dimethylamino)Phenyl)Acryloyl)-4-Hydroxy-2H-Chromen-2-One

- Activates CREB-Mediated Neuroprotection in A β and Tau Cell Models of Alzheimer's Disease." *Oxidative medicine and cellular longevity*, 2021; 1: 3058861.
12. De Sousa, Natália F., Luciana Scotti, Érika Paiva de Moura, Mayara dos Santos Maia, Gabriela CS Rodrigues, Herbert Igor Rodrigues de Medeiros, Simone Mendes Lopes, and Marcus Tullius Scotti. "Computer aided drug design methodologies with natural products in the drug research against Alzheimer's Disease." *Current Neuropharmacology*, 2022; 20(5): 857-885.
 13. Daina, Antoine, Olivier Michielin, and Vincent Zoete. "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules." *Scientific reports*, 2017; 7(1): 42717.
 14. Farihi, Ayoub, Mohamed Bouhrim, Fatiha Chigr, Amine Elbouzidi, Nouredine Bencheikh, Hassan Zrouri, Fahd A. Nasr, Mohammad Khalid Parvez, Ahmad Alahdab, and Ahmed Omar Touhami Ahami. "Exploring medicinal herbs' therapeutic potential and molecular docking analysis for compounds as potential inhibitors of human acetylcholinesterase in Alzheimer's disease treatment." *Medicina*, 2023; 59(10): 1812.
 15. Feinstein, Douglas L., Kamil Gierzal, Asif Iqbal, Sergey Kalinin, Richard Ripper, Matthew Lindeblad, Alexander Zahkarov et al. "The relative toxicity of brodifacoum enantiomers." *Toxicology letters*, 2019; 306: 61-65.
 16. Goodsell, David S., Michel F. Sanner, Arthur J. Olson, and Stefano Forli. "The AutoDock suite at 30." *Protein Science*, 2021; 30(1): 31-43.
 17. Ghadimi, Saied, Seyed Latif Mousavi, and Zahra Javani. "Synthesis, lipophilicity study and in vitro evaluation of some rodenticides as acetylcholinesterase reversible inhibitors." *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2008; 23(2): 213-217.
 18. Hindam, Merhan O., Rabab H. Sayed, Krystyna Skalicka-Woźniak, Barbara Budzyńska, and Nesrine S. El Sayed. "Xanthotoxin and umbelliferone attenuate cognitive dysfunction in a streptozotocin-induced rat model of sporadic Alzheimer's disease: The role of JAK2/STAT3 and Nrf2/HO-1 signalling pathway modulation." *Phytotherapy Research*, 2020; 34(9): 2351-2365.
 19. Huey, Ruth, Garrett M. Morris, and Stefano Forli. "Using AutoDock 4 and AutoDock vina with AutoDockTools: a tutorial." *The Scripps Research Institute Molecular Graphics Laboratory*, 2012; 10550: no. 92037.1000.

20. Haji Ali, Sazan, Derya Osmaniye, Begüm Nurpelin Sağlık, Serkan Levent, Yusuf Özkay, and Zafer Asım Kaplancıklı. "Design, synthesis, and evaluation of novel 2 H-Benzo [b][1, 4] thiazin-3 (4 H)-one derivatives as new acetylcholinesterase inhibitors." *Molecules*, 2022; 27(7): 2121.
21. Hornick, A., A. Lieb, N. P. Vo, J. M. Rollinger, H. Stuppner, and H. Prast. "The coumarin scopoletin potentiates acetylcholine release from synaptosomes, amplifies hippocampal long-term potentiation and ameliorates anticholinergic-and age-impaired memory." *Neuroscience*, 2011; 197: 280-292.
22. Huang, Ying, Xiangping Liao, Huaiwei Wang, Jianghong Luo, Shanquan Zhong, Ziliang Zhang, Fang Zhang, Jianping Chen, and Fuhua Xie. "Effects of imperatorin on apoptosis and synaptic plasticity in vascular dementia rats." *Scientific Reports*, 2021; 11(1): 8590.
23. Hadipour, E., Khodadadi M, Emami SA, Rahamouz Haghighi S, Ramazani E, Tayarani-Najaran Z. *Protective effect of Auraptene, a novel acetylcholinesterase inhibitor, on hydrogen peroxide-induced cell toxicity in PC12 cells. Biomed Pharmacother*, 2023; 164: 114997.
24. Joshi, Tanuja, Tushar Joshi, Priyanka Sharma, Hemlata Pundir, and Subhash Chandra. "In silico identification of natural fungicide from Melia azedarach against isocitrate lyase of Fusarium graminearum." *Journal of Biomolecular Structure and Dynamics*, 2021; 39(13): 4816-4834.
25. Jamkhande, P. G., Barde SR, Tidke PS, Jadhav SD. *In-vitro anti-diabetic, anti-Alzheimer, anti-tyrosinase, antioxidant activities of selected coumarin and dihydroisocoumarin derivatives. Bioorg Chem.*, 2023; 141: 106872.
26. Kimura, Toshikiro, and Kazutaka Higaki. "Gastrointestinal transit and drug absorption." *Biological and Pharmaceutical Bulletin*, 2002; 25(2): 149-164.
27. Kamarudin, N. A. B. (2020). *Molecular Docking and Acetylcholinesterase Inhibitory Activity of Psoralen Derivatives (Master's thesis)*. Universiti Teknologi MARA (UiTM), Malaysia.
28. Kim, Sunghwan, Paul A. Thiessen, Evan E. Bolton, Jie Chen, Gang Fu, Asta Gindulyte, Lianyi Han et al. "PubChem substance and compound databases." *Nucleic acids research*, 2016; 44: D1 D1202-D1213.
29. Kaushik, Manish. "A review of innovative chemical drawing and spectra prediction computer software." *Mediterranean Journal of Chemistry*, 2014; 3(1): 759-766.

30. Lilienfeld, Sean. "Galantamine—a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease." *CNS drug reviews*, 2002; 8(2): 159-176.
31. Lane, Christopher A., John Hardy, and Jonathan M. Schott. "Alzheimer's disease." *European journal of neurology*, 2018; 25(1): 59-70.
32. Llorach-Pares, Laura, Alfons Nonell-Canals, Conxita Avila, and Melchor Sanchez-Martinez. "Computer-aided drug design (CADD) to de-orphanize marine molecules: finding potential therapeutic agents for neurodegenerative and cardiovascular diseases." *Marine Drugs*, 2022; 20(1): 53.
33. Mzezewa, Sheunopa C., Sylvester I. Omoruyi, Luke S. Zondagh, Sarel F. Malan, Okobi E. Ekpo, and Jacques Joubert. "Design, synthesis, and evaluation of 3, 7-substituted coumarin derivatives as multifunctional Alzheimer's disease agents." *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2021 36(1): 1606-1620.
34. Nisha, Chaluveelaveedu Murleedharan, Ashwini Kumar, Prateek Nair, Nityasha Gupta, Chitrangda Silakari, Timir Tripathi, and Awanish Kumar. "Molecular Docking and In Silico Admet Study Reveals Acylguanidine 7a as a Potential Inhibitor of β -Secretase." *Advances in bioinformatics*, 2016; 1: 9258578.
35. National Center for Biotechnology Information (NCBI). (2017). *Artemisinin. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. <https://www.ncbi.nlm.nih.gov/books/NBK548419/>
36. Orioli, Rebecca, Federica Belluti, Silvia Gobbi, Angela Rampa, and Alessandra Bisi. "Naturally inspired coumarin derivatives in Alzheimer's Disease Drug Discovery: latest advances and current challenges." *Molecules*, 2024; 29(15): 3514.
37. Rogawski, Michael A., and Gary L. Wenk. "The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease." *CNS drug reviews*, 2003; 9(3): 275-308.
38. Rosignoli, Serena, and Alessandro Paiardini. "Boosting the full potential of PyMOL with structural biology plugins." *Biomolecules*, 2022; 12(12): 1764.
39. Ruiz Vargas, Estefanía, Luciano A. Sposato, Spencer AW Lee, Vladimir Hachinski, and Lauren E. Cipriano. "Anticoagulation therapy for atrial fibrillation in patients with Alzheimer's disease: a cost-effectiveness analysis." *Stroke*, 2018; 49(12): 2844-2850.
40. Salem, Mohamed A., Barbara Budzyńska, Joanna Kowalczyk, Nesrine S. El Sayed, and Suzan M. Mansour. "Tadalafil and bergapten mitigate streptozotocin-induced sporadic Alzheimer's disease in mice via modulating neuroinflammation, PI3K/Akt, Wnt/ β -

- catenin, AMPK/mTOR signaling pathways." *Toxicology and applied pharmacology*, 2021; 429: 115697.
41. Silva, Vera LM, Rita Silva-Reis, Alexandra Moreira-Pais, Tiago Ferreira, Paula A. Oliveira, Rita Ferreira, Susana M. Cardoso et al. "Dicoumarol: From chemistry to antitumor benefits." *Chinese Medicine*, 2022; 17(1): 145.
42. Sonmez, Fatih, Belma Zengin Kurt, Isil Gazioglu, Livia Basile, Aydan Dag, Valentina Cappello, Tiziana Ginex, Mustafa Kucukislamoglu, and Salvatore Guccione. "Design, synthesis and docking study of novel coumarin ligands as potential selective acetylcholinesterase inhibitors." *Journal of enzyme inhibition and medicinal chemistry*, 2017; 32(1): 285-297.
43. Srivastava, Vivek, Ankush Yadav, and Paratpar Sarkar. "Molecular docking and ADMET study of bioactive compounds of Glycyrrhiza glabra against main protease of SARS-CoV2." *Materials Today: Proceedings*, 2022; 49: 2999-3007.
44. Salentin, Sebastian, Sven Schreiber, V. Joachim Haupt, Melissa F. Adasme, and Michael Schroeder. "PLIP: fully automated protein–ligand interaction profiler." *Nucleic acids research*, 2015; 43(W1): W443-W447.
45. Singh S, Singh DB, Gautam B, Singh A, Yadav N. *Pharmacokinetics and pharmacodynamics analysis of drug candidates*. <https://doi.org/10.1016/B978-0-323-89775-4.00001-8> 2022; 1-2.
46. Taylor, Mark J., Claudio Bandi, and Achim Hoerauf. "Wolbachia. Bacterial endosymbionts of filarial nematodes." *Advances in parasitology*, 2005; 60: 245-284.
47. Ucar, Esra, Nuraniye Eruygur, Mehmet Atas, Merve Ergul, Mustafa Ergul, and Fazli Sozmen. "Determination of inhibitory activities of enzymes, related to Alzheimer's disease and diabetes mellitus of plane tree (*Platanus orientalis* L.) extracts and their antioxidant, antimicrobial and anticancer activities." *Cellular and Molecular Biology*, 2018; 64(11): 13-19.
48. Wanji, S., Tendongfor N, Esum M, Ndindeng S, Enyong P, Taylor MJ. *Wolbachia endosymbionts of Onchocerca volvulus in Cameroon*. *Parasitol Res.*, 2004; 92(5): 401–406. <https://doi.org/10.1007/s00436-003-1051-1>
49. Wang, Yanli, Jewen Xiao, Tugba O. Suzek, Jian Zhang, Jiyao Wang, and Stephen H. Bryant. "PubChem: a public information system for analyzing bioactivities of small molecules." *Nucleic acids research*, 2009; 37(2): W623-W633.

50. Zhong, Kate, and Jeffrey Cummings. "A critical review of brexpiprazole oral tablets as the first drug approved to treat agitation symptoms associated with dementia due to Alzheimer's disease." *Expert Review of Neurotherapeutics*, 2025; 25(1): 5-13.