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ABSTRACT

The Alzheimer's Disease in today's world is one of the most leading and progressively debilitating neurodegenerative diseases characterized due to the deposition of beta-amyloid plaques, and presence of tau tangles, and neuroinflammation. Although years of research have been put into finding out a cure for this progressive disease, very little success has been achieved, thus necessitating the need for new targets to be discovered.

Triggering Receptor Expressed found on Myeloid Cells-2 (TREM2) has proven to be recognized as an important immunoreceptor which is expressed mainly on microglia innate immune cells which are found on the Central Nervous System (CNS) and they act as the brain's first responders to pathological stimuli. TREM2 acts as a vital regulatory receptor of microglial homeostasis by controlling various neuroprotective mechanisms such as phagocytosis of Amyloid-Beta deposits, regulation of neuroinflammatory processes, microglial survival/proliferation, and synapse preservation. There are many considerable evidence based on genetic studies and functional analysis which proves that a lack of function mutations or improper regulation of TREM2 signaling pathways results in poor phagocytosis, persistent neuroinflammation, and faster progression of Alzheimer's Disease (AD). In contrast to this, it also proves that enhancing TREM2 activity improves neuroprotective responses of microglial cells; hence, TREM2 is considered as an appealing candidate for pharmacological modulation to achieve disease modification therapies for AD.

In light of the increasing attention paid to natural bioactive molecules as novel neurotherapeutic agents, this study explores the ability of naturally occurring plant polyphenols as potential TREM2 regulators. Epigallocatechin Gallate (EGCG), apigenin, curcumin, and resveratrol are widely recognized to possess potent natural reductive phytocompounds, inflammation suppressing effects, the ability to pass through the Blood Brain Barrier, and neuroprotective properties.

By evaluating the molecular interactions between TREM2 and these polyphenolic compounds, a computational in silico approach employing molecular docking was adopted in the present study. The 3D crystal configuration of TREM2 (PDB ID: 5ELI) was derived from the RCSB PDB i.e Protein Data Bank and used as the macromolecular target. In Silico docking activation were stimulated to systematically Evaluate the binding energies, interaction patterns and structural complementarity of EGCG, apigenin, curcumin, and resveratrol within the TREM2 binding site.

The docking analysis revealed a distinct hierarchy of binding affinities among the four polyphenols. Apigenin exhibited the highest binding affinity of −8.6 kcal/mol followed closely by EGCG at −8.5 kcal/mol, indicating that both compounds form thermodynamically favorable, stable, and highly specific interactions with TREM2. The strong binding energies observed for apigenin and EGCG suggest their capacity to engage critical residues within the TREM2 active site through multiple non-covalent interactions, H-bond mediated stabilization, apolar molecular contacts, and van der Waals forces, thereby stabilizing the receptor-ligand complex. Curcumin exhibited a moderate binding affinity of −7.1 kcal/mol, indicating reasonable but comparatively weaker interaction, while resveratrol recorded the lowest binding affinity of −6.3 kcal/mol among the tested compounds, suggesting limited binding efficiency with TREM2.

The superior binding affinities of apigenin and EGCG highlight their strong potential to modulate TREM2 receptor activity and, consequently, influence downstream microglial functional responses central to AD pathology — most notably neuroinflammation regulation

and amyloid-β phagocytic clearance. These findings suggest that both apigenin and EGCG can be taken as lead phytochemical scaffolds for the evolution of TREM2-targeted neuroprotective therapeutics.

While the results of this in silico molecular docking study are preliminary in nature, they provide a robust computational foundation and mechanistic rationale for advancing these polyphenolic candidates into subsequent stages of experimental validation, including in silico binding, cell-based operative studies in microglial models, and ultimately in vivo preclinical investigations. Collectively, this study contributes meaningful insights into the therapeutic modulation of TREM2 signaling through natural polyphenols and paves new pathways for the advancement of effective, plant-based interventional strategies for Alzheimer's disease.

INTRODUCTION

We know that Alzheimer's disease (AD) is the main form of dementia and is known to be one of the major public health challenges in this century. AD is a disease which is irreversible, progressively neurodegenerative, the part of our brain that is responsible for memory is affected, leading to an irreversible decline in cognitive function. This Alzheimer disease causes loss of memory, failure to comprehensive decision, thinking and learning, leading to individuals being unable to carry out daily activities that require independence. The disease was first described by a German psychiatrist, Alois Alzheimer in 1906. For decades it was thought that the disease only occurred in middle aged individuals, but in fact it is a disease that affects older people and is now recognized as the most common cause of age-related cognitive decline in the world.[1]

Al International have reported that about 55 million people in the world who are suffering from with dementia worldwide. And about 60 million peoples are suffering from Alzheimer's disease (AD) resulting to become an epidemic globally. The World Health Organization and Alzheimer's Disease80 percent of them have Alzheimer's disease. This number is expected to explode by 2050 to In India, according to the Dementia India Report, there are 5.3 million people with dementia and this number is expected to double in the next two decades putting a tremendous strain on patients, their families and healthcare systems across the country.

In Alzheimer's disease, the clinical presentation follows a number of stages [13]. In the first stage, which is called the pre-clinical or pre-symptomatic stage of the disease, changes such as amyloid-beta (Aβ) plaques and neurofibrillary tau tangles form in the brains of individuals with Alzheimer's, usually a decade or more before symptoms become apparent. As the disease progresses to the stage of mild cognitive impairment (MCI), individuals with the condition experience small but noticeable decreases in their memory and cognitive function. In the fully established dementia stage, patients exhibit profound memory loss, disorientation, language deficits, changes in personality and behaviour, and ultimately a complete loss of independent functioning.

Although over 100 years of intensive research have been conducted, till now there is still no cure for Alzheimer's disease, and available drugs so far have only a symptomatic effect. Immunotherapy strategies against amyloid-beta that have been developed more recently (such as aducanumab and lecanemab) have shown some ability to reduce amyloid levels, but their clinical effectiveness and safety are still up for debate (Chen et al., 2025; Zuo et al., 2021). This therapeutic void highlights the importance of the discovery and validation of new molecular targets and therapeutic approaches for AD.

1.2 Biochemical Mechanisms Underlying Alzheimer's Disease

There are few major features of AD but two major features of Alzheimer's disease have been identified: extracellular senile plaques, which mainly contain aggregates of amyloid-beta peptides, and intracellular neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau protein. In addition to these classical features, recent research has led to the appreciation that the disease pathogenesis is a complex, highly interrelated and self-perpetuating process involving neuroinflammation, synaptic dysfunction, mitochondrial impairment, oxidative stress, and disrupted proteostasis.

The amyloid precursor protein (APP) is sequentially cleaved by beta-secretase (BACE1) and gamma-secretase enzyme complexes to form amyloid-beta peptides. In a healthy brain, soluble Aβ monomers are promptly eliminated from the brain via several pathways, such as enzymatic degradation, CSF drainage, and receptor-mediated transcytosis across the blood-brain barrier. In the Alzheimer brain, this equilibrium is disturbed either by excess production of Aβ (as in familial early-onset cases caused by

mutations in the APP, PSEN1 and PSEN2 genes) or by impaired clearance (as is dominant in the late onset sporadic form) resulting in progressive accumulation of oligomeric and fibrillar Aβ species that combine into mature plaques.

In normal biology, tau protein is a cytoskeleton protein that wok as stabilizing agent for the cytoskeletal elements of the axons and their transportation machinery. In the pathological state of AD, there is abnormal hyperphosphorylation of the tau protein, to the detachment of microtubules and ultimately aggregation into NFTs via formation of paired helical filaments [15]. Pathological evolution of the tau protein follows a consistent pattern in the brain, first developing in the entorhinal cortex and hippocampus before moving to limbic and neocortex regions.

Neuroinflammation has come to be recognized as a third central pathological feature of Alzheimer's disease, instead of being a minor epiphenomenon. Bra [1]sident innate immune cells called microglia constantly patrol the neural parenchyma. Microglia can be activated and trigger inflammatory responses in the context of Aβ deposition and neuronal injury, which may be beneficial and protective in the acute phase by facilitating the phagocytosis of amyloid and tissue repair. However, prolonged and chronic activation leads to a pro-inflammatory dysfunctional state of microglia, with the excessive production of cytokines (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6)), reactive oxygen species (ROS) and antioxidant, which further contributes to neuronal injury and disease progression [5],[6].

1.3 TREM Cells 2: A Central Controller of Microglial Function in Alzheimer's Disease

The TREM2 is one of the most important and promising targets discovered over the last ten years among the molecular pathways involved in microglial function in Alzheimer's disease. TREM2 is an immunoglobulin superfamily type 1 transmembrane receptor, mainly expressed by microglia in the CNS, and by peripheral myeloid cells like macrophages, osteoclasts and dendritic cells, [6],[7].

Two to four-fold risk variants in the TREM2 gene were discovered and in particular the R47H missense variant, which put TREM2 in the spotlight of the genetic research on AD [18]. This risk size is similar to the well-known genetic risk factor for sporadic Alzheimer's disease, the APOE4 allele, which indicates the crucial role microglial immune signalling plays in the ethology of the disease [7],[8].

TREM2 signals through its transmembrane adaptor protein DAPI12 kDa which contains an immunoreceptor tyrosine-based activation motif (ITAM). Ligands binding to the extracellular immunoglobulin-like domain of TREM2 recruit and activate Syk kinase through the activation of ITAMs that are phosphorylated by Src-family kinases; this activates downstream signaling pathways. These pathways together control a wide range of microglial activities, such as phagocytosis, chemotaxis, production of inflammatory cytokines, cellular metabolism, proliferation and survival [7],[8],[9].

TREM2 is involved in several critical protective activities in the context of Alzheimer's disease. It encourages phagocyte-mediated removal of amyloid-beta aggregates, apoptotic neurons, and cellular debris, and restricts propagation of amyloid-beta toxic protein aggregates. TREM2 also contributes to the metabolic fitness of DAM, a transcriptionally distinct microglial state that is associated with genes involved in phagocytosis, lipid metabolism and lysosome function that is observed in the vicinity of amyloid plaques and is thought to represent a protective adaptive response to Aβ deposition. Loss of TREM2 function impairs the shift into this DAM state, reduces amyloid clearance and causes chronic, unremitting neuroinflammation, accelerating neurodegeneration [8],[9],[19].

For these complex protective functions, TREM2 has been a target of interest in the field of Alzheimer's disease, and strategies to boost TREM2 signalling, to block the shedding of the TREM2 ectodomain (to generate soluble sTREM2) and to stabilize the TREM2-DAP12 receptor complex are currently being explored. Nevertheless, small molecule modulators of TREM2, especially of natural origin, are under-studied and hold great potential for computational and experimental drug discovery efforts [9].

1.4 Natural Polyphenols as Neuroprotective Agents

Natural polyphenols are a huge and largely diverse group of plant secondary metabolites, which are defined by the presence of one or more phenolic hydroxyl groups in aromatic ring systems. To date,

over 8000 polyphenolic compounds have been identified in the plant kingdom and these include flavonoids, stilbenes, phenolic acids, lignans, tannins, and others. The polyphenols are widely found in food and beverages such as fruits, vegetables, legumes, whole grains, tea, coffee, red wine and spices, and have been linked to a wide range of health benefits in many epidemiological and experimental studies .

Polyphenols have been the focus of many studies in the context of neurodegenerative diseases due to their ability to act on several pathological mechanisms involved in Alzheimer's disease. These include powerful antioxidant activity by directly scavenging free radicals and induction of endogeneous antioxidant defense bio enzymes activity by modulation of NF-κB and MAPK signalling pathways, inhibition of Aβ aggregation and promotion of disaggregation of preformed fibrils, inhibition of BACE1 and gamma-secretase activities, inhibition of tau hyperphosphorylation, modulation of autophagy and mitophagy, and the protection of synaptic structure and function [3],[4],[5].

Epigallocatechin-3-gallate (EGCG), apigenin, curcumin and resveratrol are some of the most widely studied phytochemicals with neuroprotective properties in various chemical classes. The most abundant and bioactive catechin in green tea (Camellia sinensis) is EGCG, which belongs to the subclass of flavonoids known as flavan-3-ols, and has been shown to have strong anti-amyloidogenic, anti-tau, antioxidant and anti-neuroinflammatory properties in many in vitro and in vivo models [3]. Apigenin is found in edible plants such as chamomile, parsley, and celery and is a flavone that crosses the blood brain barrier, regulates neuroinflammatory signaling and promotes neurogenesis in the hippocampus [4]. The rhizome of turmeric are found to contain curcumin, which has a number of properties that have been shown to reduce Aβ aggregation, disaggregate preformed fibrils, chelate metal ions that are thought to mediate Aβ toxicity and attenuate neuroinflammation [4],[5]. Resveratrol is a stilbene polyphenol present in grapes, red wine, berries, and peanuts that has been shown to activate SIRT1 deacetylase pathways, to induce autophagic clearance of Aβ, and to exert anti-inflammatory and anti-oxidative effects [4].

In spite of their promising multi-target neuroprotective activity, the clinical translation of these polyphenols in Alzheimer's disease has been limited by their pharmacokinetic drawbacks such as low aqueous solubility, low oral bioavailability, rapid metabolism and inadequate blood brain barrier penetration. However, they possess a wealth of biological functions and are proven safe for use, which renders them appealing targets for structure-activity relationship analysis and computational screening to discover specific molecular interactions with proven AD targets like TREM2 [3],[4],[10]

1.5 Molecular Docking as a Computational Drug Discovery Tool

The rational identification of drug candidates that interact favourably with a biological target of interest has been fundamentally transformed by the advent of computational methods in medicinal chemistry and structural biology. Of these, Insilco docking is one of the mostly used and powerful tools in the current drug discovery pipelines. Molecular docking is a computational simulation method which can predict the preferred binding position (pose) of a small ligand in the 3d binding position of a macromolecular target (receptor) and calculated free energy of binding associated with this orientation as a binding affinity or a docking score (kcal/mol) [11].

Docking algorithms proceed by systematically sampling the conformational space of a flexible ligand in a specified search space on the receptor, scoring the geometric and energetic fit between each pose of the ligand and the receptor, and ranking the poses based on the calculated binding affinity. The most common docking programs are AutoDock, AutoDock Vina, DOCK, Glide, GOLD, and FRED which use different algorithms for searching for binding sites and different scoring functions to determine the binding affinity. The platform used in the present study is AutoDock Vina, which is faster and more accurate than its predecessor AutoDock 4 [11] and uses a gradient optimization method to determine a docking pose and a sophisticated empirical scoring function that considers steric, hydrophobic and hydrogen-bonding interactions.

Molecular docking has several promising benefits in drug discovery for neurodegenerative diseases. It allows for screening of large compound libraries against a target of interest quickly and cost effectively

and is used to prioritise the most promising candidates for experimental testing, thereby saving time and resources from traditional high throughput experimental screening. The information it provides is also invaluable in understanding structure-activity relationships and hit-to-lead optimization, giving atomic-level understanding and insights into the key non-covalent interactions that mediate ligand-receptor recognition, such as conventional covalent and non-covalent bond.[11],[12].

In some Alzheimer's disease and neuroinflammation studies, molecular docking has given valuable insights regarding the potential interactions between natural compounds and known targets like acetylcholinesterase, BACE1, gamma-secretase, GSK-3β, HDAC, and, more recently, immune receptors such as TREM2. These computational investigations have shown the usefulness of in silico screening in the identification of polyphenols and other phytochemicals with favourable predicted binding characteristics, rational mechanism of action for their observed biological activity and the prioritisation of candidates for experimental follow-up [12],[21].

1.6 Objectives and Boundaries of the Present Investigation

The overall goal of this dissertation is to systematically evaluate the binding properties of selected natural polyphenols to TREM2 in silico by molecular docking to find candidate natural polyphenols that may modulate TREM2 activity and thus potentially augment microglial mediated neuroprotection in AD.

oUR study aims to:

(i) To download and structure the three-dimensional crystal structure of TREM2 (PDB ID: 5ELI) for molecular docking.

(iii) To select, retrieve and prepare the three-dimensional structures of four representative natural polyphenols (EGCG, apigenin, curcumin and resveratrol) as candidate ligands.

(iii) To conduct molecular docking studies on each polyphenol compound in the TREM2 binding site using AutoDock Vina within PyRx virtual screening software to obtain the binding affinities and binding pose of each polyphenol compound in the binding site of TREM2.

(iv) To analyse and visualise the obtained protein-ligand complexes in BIOVIA Discovery Studio Visualizer to find out the important non-covalent interactions and binding residues.

(v) To discuss the docking results in the light of the TREM2 biology and Alzheimer's disease pathology and suggest a computational rationale for selecting certain polyphenols for experimental testing as TREM2 modulators.

This study is limited to computational in silico methods, namely the molecular docking and does not include experimental laboratory validation. The findings are to be used to develop mechanistic hypotheses and prioritization frameworks that will inform future in vitro and in vivo experimental studies. The study only involves the four polyphenols with already established neuroprotective and anti-neuroinflammatory effects, and the TREM2 crystal structure with PDB ID 5ELI, which represents the extracellular immunoglobulin-like domain of human TREM2 in a conformation appropriate for the docking analysis of the ligands.

CHAPTER 2

Literature Review

2.1 AD: Epidemiology, Etiology, and Pathophysiological Mechanisms

AD is the main reason of dementia in the world and is the cause of about 60-80% of all dementia cases. The impact of the disease on the population is enormous and will keep increasing with the ageing of the global population. It that there are ~55 million people worldwide with dementia, and that this number will grow to 78 million by 2030 and 139 million by 2050. The total economic burden of dementia worldwide is estimated to be over one trillion USD dollars per year, including direct health care expenses, indirect costs due to informal care and lost productivity [1], [2].

There are two general categories of etiological forms of AD. The familial, early onset type (less than five percent of all cases) is due to autosomal dominant mutations in genes that encode the APP, PSEN1, and presenilin-2 (PSEN2), all of which lead to elevated levels of the amyloidogenic Aβ42 peptide. The sporadic and late onset type (the great majority of cases) is the result of complex interaction of a number of genetic susceptibility loci, as well as environmental factors, lifestyle and age-related biological changes. The epsilon-4 APOE4 is the most potent known genetic risk factor for sporadic AD, with a two- to three-fold increased risk in heterozygotes and an eight- to twelve-fold higher risk in homozygotes compared with the APOE3 reference allele [2], [1],[3],[17].

The neuropathological hallmark of AD is the progressive deposition of extracellular Aβ plaques and intracellular neurofibrillary tau tangles in specific brain areas, particularly in the hippocampus, entorhinal cortex, and association cortices, which result in a loss of synapses and neuroinflammation and ultimately in the death of neurons throughout the brain. The amyloid cascade hypothesis suggests that an abnormal accumulation of Aβ is the initial event in the pathogenesis of AD, leading to a cascade of events including tau pathology, synaptic dysfunction, neuroinflammation and neurodegeneration [14]. Although this concept has been the basis for most therapeutic approaches over the last 30 years, the failures of many anti-Aβ therapeutic strategies in recent clinical trials have led to a more general consensus that neuroinflammation, tau pathology, synaptic dysfunction, and metabolic abnormalities are all co-equal factors that need to be targeted [3],[5],[22].

Microglia, the innate immune cells of the brain, are the primary cells involved in neuroinflammation in Alzheimer's disease, in addition to astrocytes and infiltrating peripheral immune cells. The last ten years of GWAS have identified a remarkable number of AD risk-loci within genes that are primarily or entirely expressed in the microglial immune system, such as TREM2, CR1, CLU, CD33, INPP5D, MEF2C and many others, confirming the idea that microglial immune signaling is a primary driver of AD risk and progression, not a mere secondary consequence of neurodegeneration [5,6,7].

2.2 TREM2 in Neurodegeneration: Structure, Signaling, and Disease Relevance

The TREM2 gene encodes a 230-amino acid type I transmembrane glycoprotein of the immunoglobulin superfamily found on chromosome 6p21.1. The protein has an extracellular immunoglobulin variable (IgV) domain that is involved in recognizing the ligand, a short stalk domain, one transmembrane helix with a critical positively charged lysine for binding to the negatively charged DAP12 adaptor, and a short cytoplasmic tail [7],[8].

Structural studies of TREM2 by X-ray crystallography and cryo-electron microscopy have greatly facilitated the understanding of TREM2 function. The crystal structure of the human TREM2 extracellular domain (PDB ID: 5ELI) shows that the structure is a classical IgV-fold with a conserved disulfide bond with a positively charged surface that is expected to bind negatively charged lipid ligands and phospholipid-associated proteins that aggregate during neurodegeneration. Structural studies have shown that the major ligand binding interface is a hydrophobic groove with adjacent charged patches, which has been an important basis for computational docking investigations [7,8,9].

The ligands for TREM2 discovered so far are a wide range of molecules that reflect the receptor's function in detecting and reacting to cellular damage and lipid dysregulation during neurodegeneration. These include soluble oligomeric forms of Aβ, apolipoprotein E, clusterin, sulfated glycosaminoglycans, low density lipoprotein (LDL) and very low-density lipoprotein (VLDL), and phosphatidylserine and phosphatidylethanolamine exposed on apoptotic cell membranes [8],[9]. The diversity of these ligands indicates that TREM2 is a pattern recognition receptor involved in monitoring the lipid microenvironment and metabolic status of the brain parenchyma.

The cellular effects of the TREM2 signaling pathway have been well characterized in the context of Alzheimer's disease. Under trophozoid deprivation conditions, functional expression of TREM2 signaling can prevent microglial cell death through the activation of the PI3K-Akt-mTOR pathway and the inhibition of apoptosis. It increases the phagocytosis of microglia, leading to better internalization and degradation of Aβ aggregates and apoptotic neurons in the lysosomes. It facilitates the shift of microglial metabolic pathway to oxidation phosphorylation and fatty acid oxidation necessary for maintaining the energy-intensive disease-associated microglial state. Additionally, TREM2 signaling regulates inflammatory cytokine release, which typically leads to a more anti-inflammatory microglial phenotype that helps prevent collateral neuronal damage [8],[9].

In contrast, loss-of-function mutations of TREM2, ectodomain shedding by the metalloprotease ADAM10 and a lack of engagement with ligands have all been shown to have a spectrum of negative effects which are variously manifested as decreased clustering of microglia around amyloid plaques, decreased amyloid compaction or clearance of Aβ, increased neuritic dystrophy around plaques, increased inflammatory signaling, and increased neurodegeneration. Consistent with this, Trem2 is genetically deleted in mouse models, leading to enhanced amyloid pathology, decreased disease-associated microglia, and impaired cognition [7],[8],[9].

Several lines of evidence reinforce the translational importance of TREM2 in human AD. In addition to the genetic risk associated with R47H, R62H, and other coding variants, soluble TREM2 (sTREM2) in the CSF has been shown to be a marker of microglial activation and disease progression, and to increase with tau pathology and be correlated with clinical deterioration. Zhang et al. (2025) performed a detailed systematic review of TREM2 and sTREM2 in Alzheimer's disease, finding that sTREM2 is a dynamic biomarker of microglial reactivity to amyloid and tau pathology and that interventions that increase TREM2 signaling hold promise as disease modifying interventions [1]. In a second review, similarly performed by Yin et al. (2024), the importance of TREM2 in the regulation of neuroinflammation, phagocytosis and microglial survival was reiterated, with genetic, transcriptomic and proteomic evidence supporting a role of TREM2 in the progression of AD [2].

2.3 Natural Polyphenols in Alzheimer's Disease: Mechanisms and Evidence

Over the last 20 years, there has been a compelling body of epidemiological, preclinical and, increasingly, clinical evidence that suggests dietary and plant-derived polyphenols could provide some degree of neuroprotection against Alzheimer's disease. Several epidemiological studies have reported negative relationships between the consumption of polyphenol-rich dietary patterns, such as the Mediterranean diet and its variations, and cognitive decline and dementia in elderly people. These led to extensive mechanistic studies of specific polyphenolic compounds and their molecular targets and biological activities in models of AD [3],[4],[10],[20].

2.3.1 EGCG

They are mostly in green tea is EGCG and the most widely studied anti-Alzheimer polyphenol. Chemically EGCG (C22H18O11, molecular weight 458.37 g/mol) is a flavan-3-ol which is esterified with gallic acid and contains several catechol and galloyl hydroxyl groups responsible for its high antioxidant and metal-chelating properties. EGCG has been found to disrupt the secondary structure of Aβ, specifically by disrupting beta-sheet structure, to disaggregate preformed Aβ fibrils, to chelate transition metal ions (copper, zinc, iron) that are known to be involved in Aβ oligomerization, and to inhibit BACE1 activity [3],[4].

EGCG is found to stop the working of NF-κB, and cause the decrease expression of COX-2 and iNOS , and stop the production of TNF, IL-1beta and IL-6 in cellular and animal models. Vicente-Zurdo et al. (2024) performed a thorough analytical review of polyphenols for their neuroprotective properties, summarizing the multi-target activity profile of EGCG, including the inhibition of amyloid, anti-tau, antioxidant, and anti-neuro-inflammatory properties [3]. Dietary supplementation with EGCG has been shown to decrease amyloid plaque burden, decrease levels of neuroinflammatory markers, and improve cognitive deficits in behavioral paradigms in several studies using APP/PS1 and 3xTg-AD transgenic mouse models [3, 4].

2.3.2 Apigenin

Apigenin is one of the flavones present in high concentrations in the flowers of chamomile, but also in parsley, celery and many other edible plants. Apigenin has been the subject of much research in the field of Alzheimer's disease because of its unique pharmacokinetic characteristics compared to other polyphenols, such that it can cross the blood-brain barrier, its metabolic stability and its low toxicity profile [4].

Apigenin has a number of mechanisms of action for its anti-neuroinflammatory activity, including effects on NF-κB and MAPK/ERK signaling ways, as well as blocking microglial activation markers. A review by Özge Şahin et al. (2025) reported that apigenin has been shown to have neuroprotective properties in neurodegenerative diseases, suggesting that its multi-target activity and anti-neuroinflammatory and anti-amyloidogenic effects render it a promising therapeutic agent [4]. In particular, apigenin has been shown to regulate microglial function and inflammatory signaling pathways, making it a promising candidate for further study as a potential TREM2 modulator.

2.3.3 Curcumin

Turmeric (Curcuma longa) is a spice that has been used for centuries as medicine, and curcumin is the primary polyphenolic pigment found in turmeric. Curcumin has received extensive preclinical studies and a few clinical trials and has been one of the most widely studied polyphenols Alzheimer's disease studies [4],[5].

Curcumin's anti-Alzheimer mechanisms are very wide-ranging. It directly binds to and inhibits the aggregation of both Aβ and tau, disaggregates preformed Aβ aggregates, chelates metal

ions, inhibits BACE1 and gamma-secretase activity, activates Nrf2-mediated antioxidant responses, and has potent antioxidant effects by stopping NF-κB, AP-1 and STAT3 signaling pathways. In particular, Chen et al. (2025) performed a detailed review on the polyphenols such as curcumin for Alzheimer's disease, which included a comprehensive analysis of molecular and therapeutic mechanisms based on in silico data [5]. Even with these promising preclinical characteristics, the clinical use of curcumin has been limited by very polarity, low oral bioavailability and rapid metabolic inactivation that has led to the development of interest in the formulation of curcumin into nanoparticles and the development of structural analogues that have better pharmacokinetic properties [4],[5].

2.3.4 Resveratrol

Resveratrol is a stilbene polyphenol that is synthesized by many plant species as a defense mechanism against stress, injury and pathogen attack, and is especially rich in the skin of red grapes, red wine, berries and peanuts. The involvement of resveratrol in the start of the NAD-dependent deacetylase SIRT1, a central control point for cellular metabolism, stress response and longevity pathways, is the primary reason for the extensive research into its role in anti-aging and other diseases related to health.

In AD models, resveratrol has been shown to have neuroprotective properties by inducing deacetylation and activation of SIRT1, which leads to the removal of misfolded tau and the clearance of Aβ oligomers by autophagy. It also has an effect on AMPK signaling, inhibits the activation of NF-κB and NLRP3 inflammasome, prevents mitochondrial dysfunction, and regulates APP processing to decrease Aβ production. Resveratrol, as modulators of neuroinflammation and neurodegeneration in Alzheimer's disease and its capacity to regulate microglial activation states and inflammatory signaling networks [10]. In mild to moderate AD, clinical trials of resveratrol have shown to be generally safe and well-tolerated, with some evidence of its effects on CSF Aβ40 levels and neuroinflammatory biomarkers, but efficacy outcomes have been inconsistent [4],[10].

2.4 Molecular Docking in Neuropharmacology: Methods and Applications

The molecular docking technique has become an indispensable tool in drug discovery for neurodegenerative diseases, allowing the identification of lead compounds and mechanistic characterization of interactions between these compounds and disease-relevant protein targets, in a rapid and cost-effective way. The methodological framework of molecular docking involves three related computational problems: the conformational and positional search algorithm for samples; the scoring function that assesses and ranks samples; and the protein representation that captures the structural features that are important for ligand binding [11],[12].

Developed at the Scripps Research Institute by Trott and Olson and published in 2010, AutoDock Vina is based on an iterated local search global optimizer, a gradient optimizer for pose refinement, and an empirical scoring function that is calibrated using experimental protein-ligand co-crystal structures and binding affinity data. The scoring function predicts binding as a combination of steric (repulsive/dispersive) and hydrophobic and hydrogen bonding components in kcal/mol, with more negative scores predicting stronger binding [11]. In this present study, the program PyRx was used as a graphical interface of AutoDock Vina which is a platform for 3D protein preparation, docking and analysis of docking results, thus significantly decreasing technical barriers to HTS-VS [11].

A key issue is whether the molecular docking predictions are valid or not, which relies heavily on the quality of the input protein structure, the completeness and accuracy of the ligand

preparation (including the appropriate protonation states and torsional definitions), and the selection of an appropriate search space (grid box) that covers the biologically relevant binding site adequately. For proteins with poorly defined binding sites from experimental data, blind docking over the whole protein surface (as used here) is an unbiased method for determining the preferred binding site [11],[12].

Comprehensive characterization of the interactions like non covalent bond between ligand and receptor in top-ranked docking poses is possible after post-docking analysis in visualization software like BIOVIA Discovery Studio Visualizer. These interactions involve conventional hydrogen bonds, carbon-hydrogen bonds, hydrophobic contacts, van der Waals interactions, pi-cation (aromatic rings with positively charged residues) interactions, pi-pi stacking (face-to-face and T-shaped) interactions and halogen bonds, all of which add differently to binding affinity and selectivity [12].

Within the field of TREM2 and neuroinflammation research, Ulland and Colonna (2020) reviewed TREM2's role in microglial biology and in the context of Alzheimer's disease, elaborating on TREM2's structural and functional role as a druggable target and discussing ways to modulate its function in the context of AD [7]. It was extensively reviewed the physiology, pathology and therapeutic potential of the TREM2 signaling pathway, offering mechanistic support for targeting TREM2 in neurodegeneration [8]. In AD mouse models, showed that pharmacological modulation of TREM2 activity alters microglial responses and amyloid pathology, supporting the concept of TREM2 as a modifiable therapeutic target [9].

Computational docking studies have been conducted previously to gain insight into the interactions of natural compounds with TREM2; however, the field is still in its early stages. We found that both investigated the molecular mechanisms and in silico data for polyphenols as neuroprotective agents in Alzheimer's disease, providing insights into the role of docking in understanding protein-ligand interactions and predicting bioactivity [3],[4]. In the context of Alzheimer's disease, specifically investigated polyphenolic compounds with the support of in silico methods, which is closely related to the computational methods used in the current study [5]. Together, these publications present the scientific justification and methodological precedent for the in-silico assessment of natural polyphenols as TREM2 modulators carried out in this dissertation.

2.5 Gap Analysis and rationale for the present study.

Although the pathological importance of TREM2 dysfunction in AD has been well established, and the neuroprotective role of polyphenolic compounds has been corroborated by numerous publications, the interaction between molecules like polyphenolic compounds and the TREM2 protein have never been systematically characterized by computational docking analysis. Previous molecular docking investigations of polyphenols for AD have been mostly directed toward the classical enzymatic targets (acetylcholinesterase, BACE1, and GSK-3β), and with only a few studies targeting immune receptor targets (TREM2) [3],[4],[5].

In addition, although the genetic and functional evidence for TREM2 as a primary regulator of risk and progression of Alzheimer's disease is undeniable, and several biopharmaceutical strategies to enhance TREM2 signaling are in the preclinical and early clinical development, the possibility of naturally occurring small molecules that can modulate TREM2 function remains unexplored. Given the multi-target neuroprotective properties, the excellent safety profiles, brain permeability, and anti-neuroinflammatory effects of natural polyphenols, this class of compounds is an interesting group of potential TREM2 modulators that should be explored systematically using computational tools [7],[8],[9].

To fill this gap, the present study aimed to systematically analyze the molecular docking of four representative polyphenols (EGCG, apigenin, curcumin, and resveratrol) with the TREM2 crystal structure using both binding affinity and binding pose as criteria, as well as to identify major interacting residues and to interpret the results in the light of TREM2 biology and Alzheimer's disease pathogenesis. The results will be used to offer a mechanistic computational reason for prioritizing candidate polyphenols to be further validated through experimental testing in cell-based and animal models of Alzheimer's disease.

CHAPTER 3

METHODOLOGY

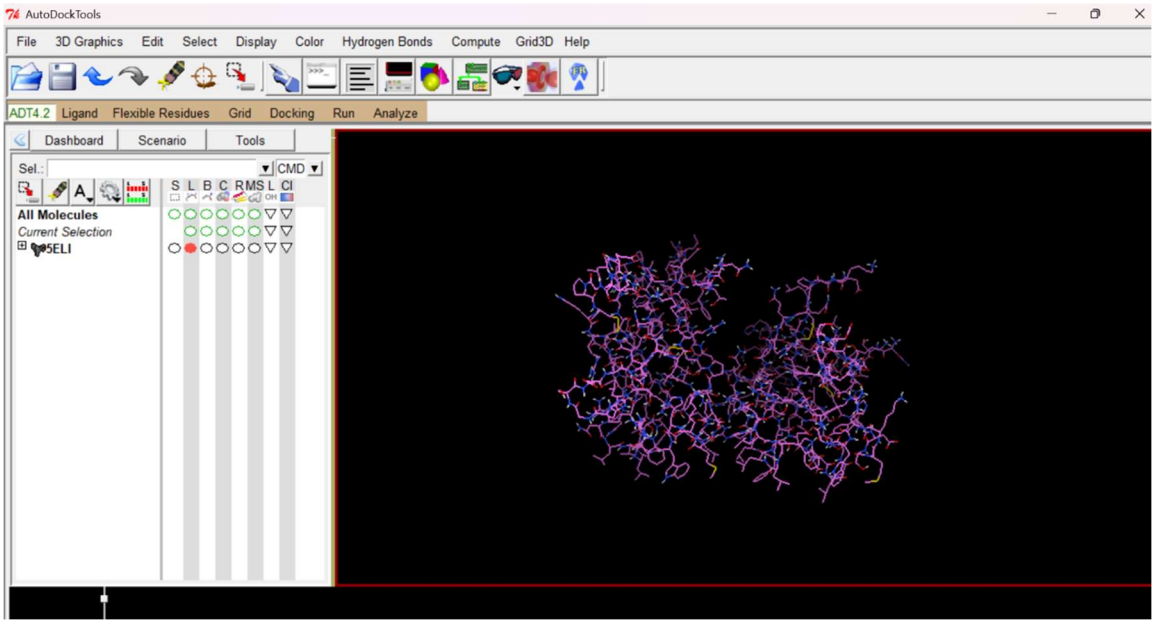
This study utilizes molecular docking to evaluate the binding interactions between TREM 2 and a panel of commonly used Natural plant-derived polyphenols for example epigallocatechin gallate (EGCG), apigenin, curcumin, and resveratrol to predict their potential to stabilize IL-11 through favorable interactions. Here, we used PyRx for virtual screening of multiple excipients (ligands) targeting TREM 2. The following paragraphs detail the approach utilized for ligand selection, protein preparation, molecular docking, and validation procedures.

3.1 How to retrieve protein and preparation

• The 3D TREM2 was retrieved From the AlphaFold Protein structure Database. The predicted structure was produced from the AlphaFold2 deep learning model created by DeepMind and EMBL-EBI.

• The prediction confidence for every residue was eliminated using the pLDDT scores provided. Regions with low confidence were visually checked and, if necessary, were removed from docking studies to maintain the reliability of interaction predictions.

• We will use Auto Dock Tools, and all water molecules and heteroatoms were removed. We will also assigned Polar hydrogens and Gasteiger charges .The protein was stored in PDBQT format for docking.



Screenshot showing loading of protein in Auto Dock 4.0

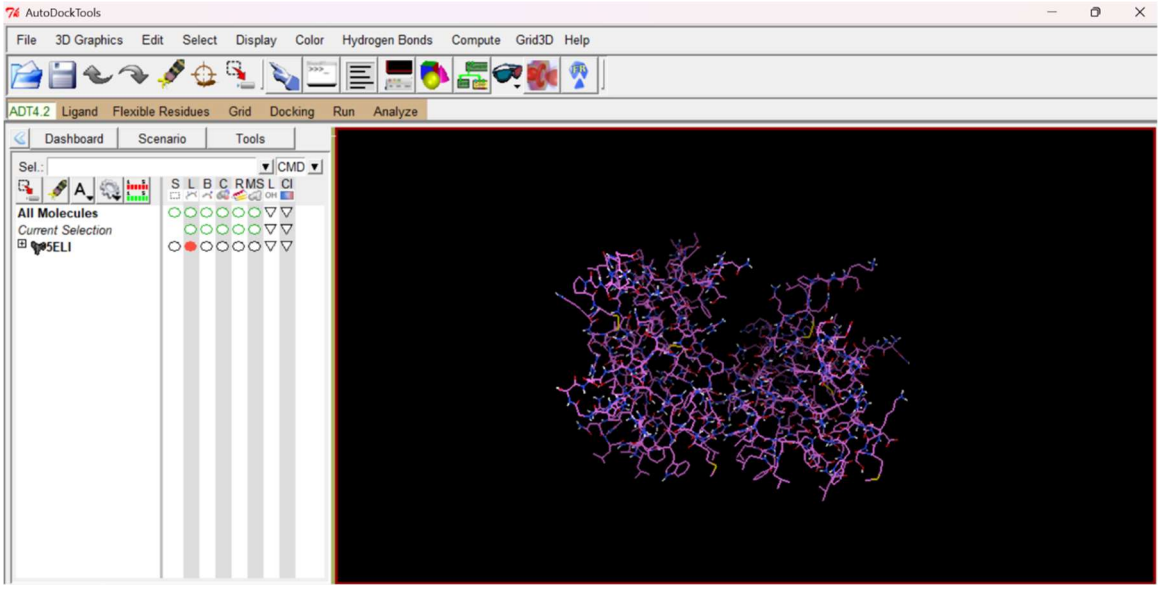


Fig 3.2: Screenshot showing protein after modification

1. Download the ligand

Visit PubChem at www.pubchem.ncbi.nlm.nih.gov.

• 3D Structures of EGCG, Apigenin, Curcumin, Resveratrol, were fetched from PubChem (https://pubchem.ncbi.nim. nih.gov/in) in SDF format and were converted into PDBQT format using Auto Dock Tools.

• Geometry optimization and torsion tree definitions were applied to prepare flexible ligand

2.Performing docking using pyrx

Auto dock Vina will be the docking tool that we use. We use the Vina algorithm to dock it in Pyrx. Launch Pyrx GUI and followed the steps given below:

2.1Protein Loading

• Select "File" -> "Load Molecule" or simply click the first icon in the upper left corner. Choose the protein structure that you downloaded. referred to here as "TREM 2"

• Convert pdb format of protein to pdbqt by right clicking on TREM 2 then on display and now select macromolecule.

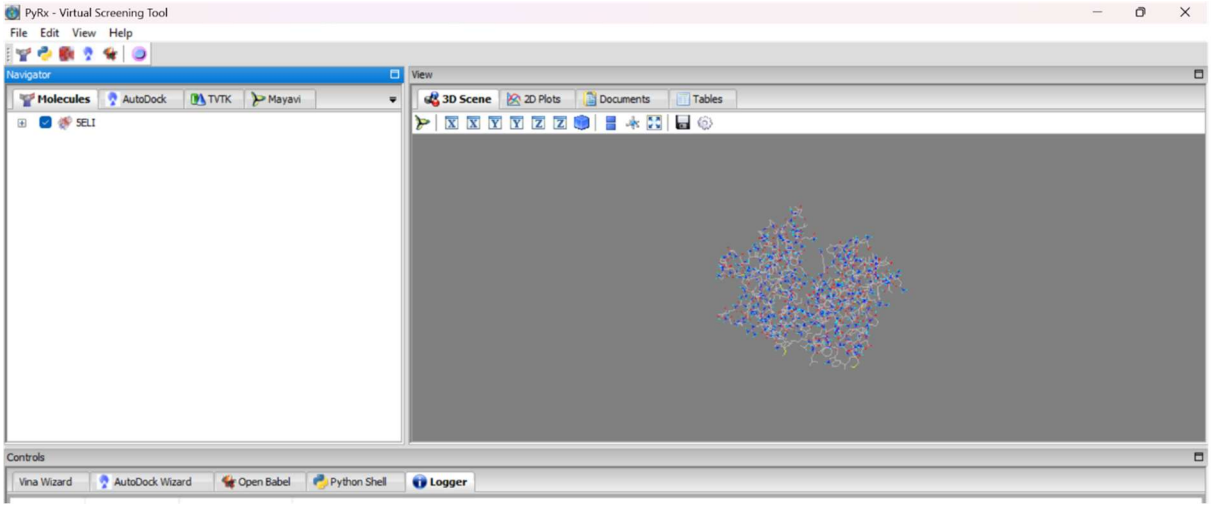


Fig 3.3 Screenshot showing conversion of protein file pdb to pdbqt

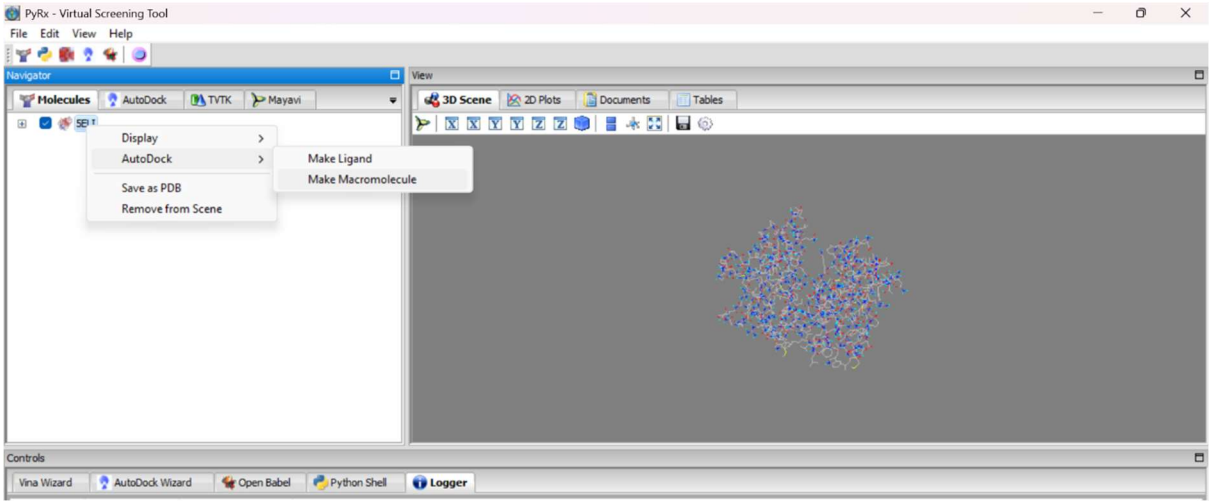


Fig 3.4 Conversion of protein file pdb to pdbqt

2.2 Ligand loading

• In PyRx, click on OpenBabel and select on insert new item present on bottom right corner.

• Now select each ligand from folder one by one and upload it.

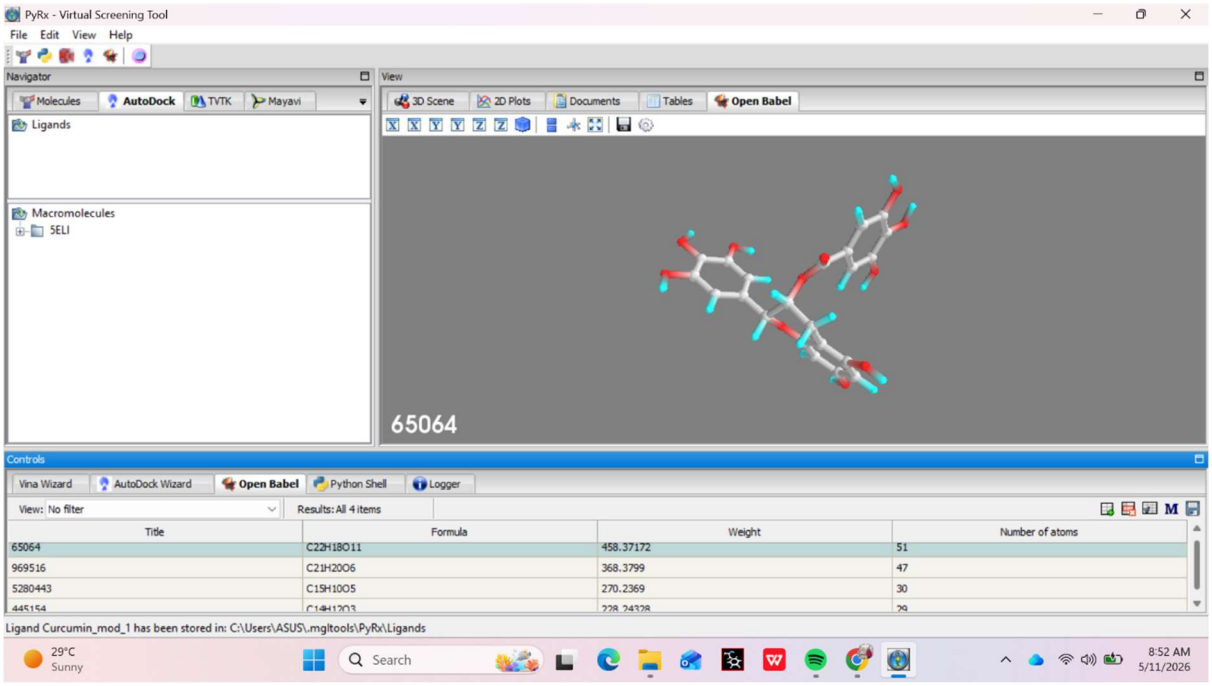


Fig 3.5: Screenshot showing loading of ligands

• After uploading all ligands, right click on ligand and select minimize all to decrease the energy.

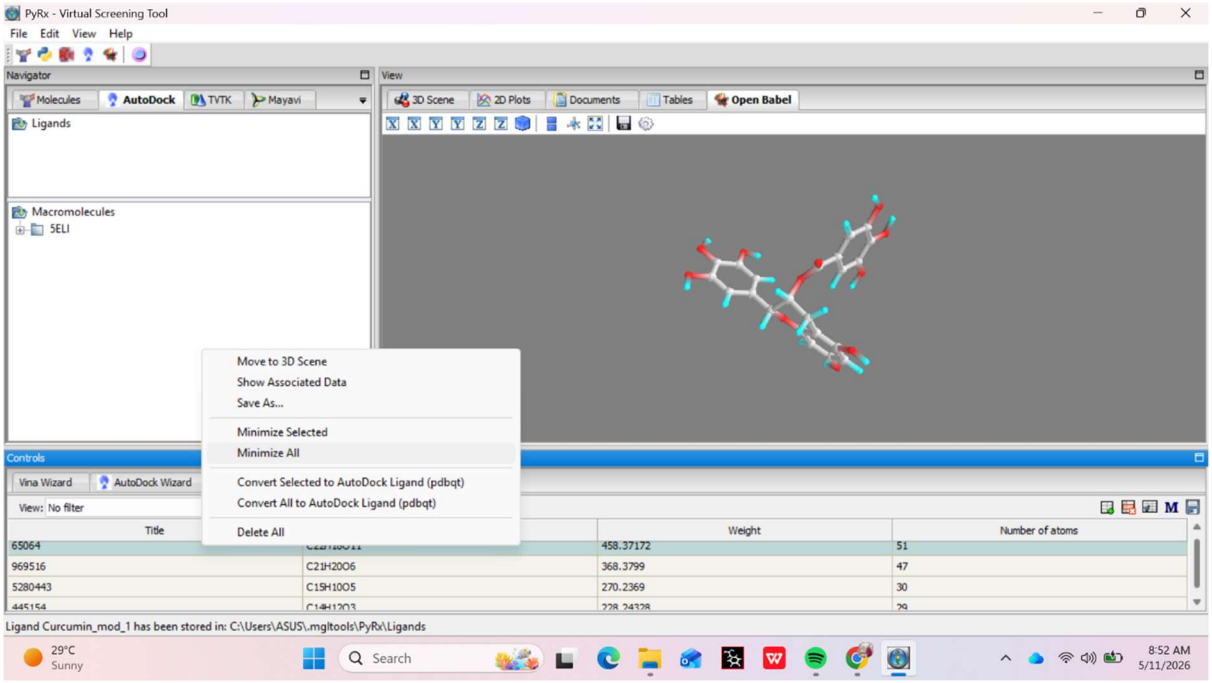


Fig 3.6: Screenshot showing minimization of energy of ligand

• Again, right click and select convert all to AutoDock ligand (pdbqt) to convert all ligands to pdbqt format.

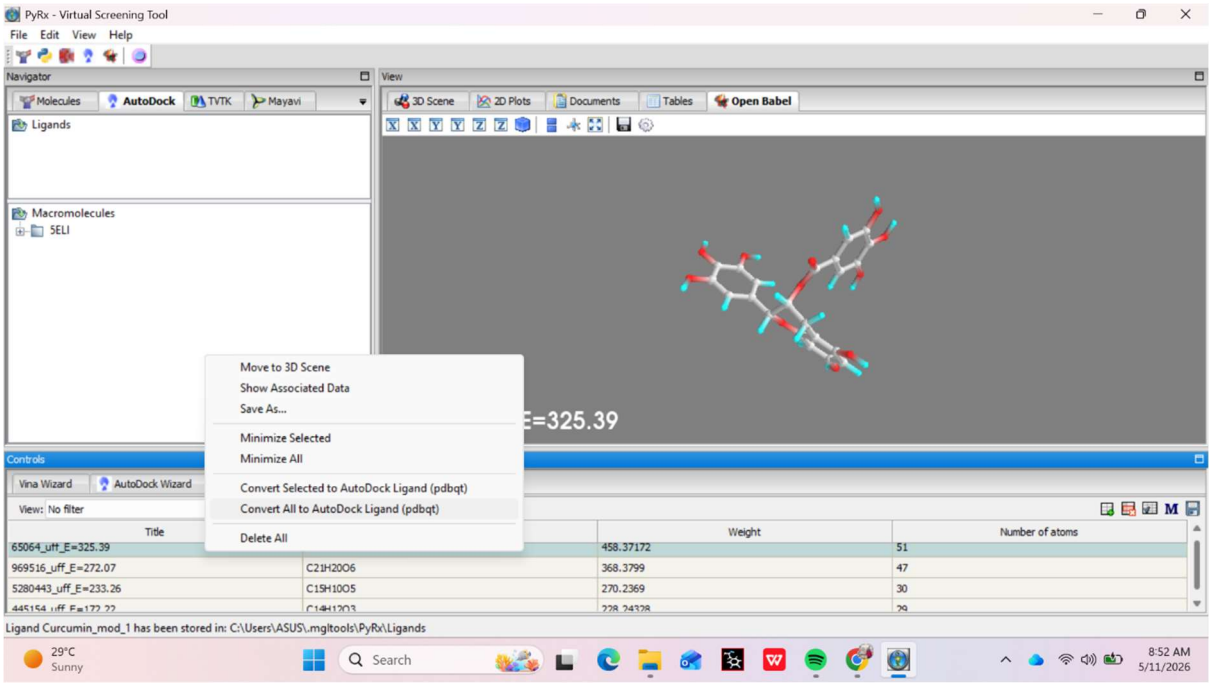


Fig 3.7: Screenshot showing conversion of all ligands to pdbqt

3 Defining ligands and proteins

The loaded protein and ligand are shown under the "Molecules" tab. It is now necessary to identify which is a ligand and which is a protein. • Right-click on the protein –> “Autodock” > “Make Macromolecule” to accomplish that. Perform a right-click on the ligand, select "Autodock," then "Make Ligand."After that, you'll see that it has automatically prepared their PDBQT files under the 'Autodock' page.

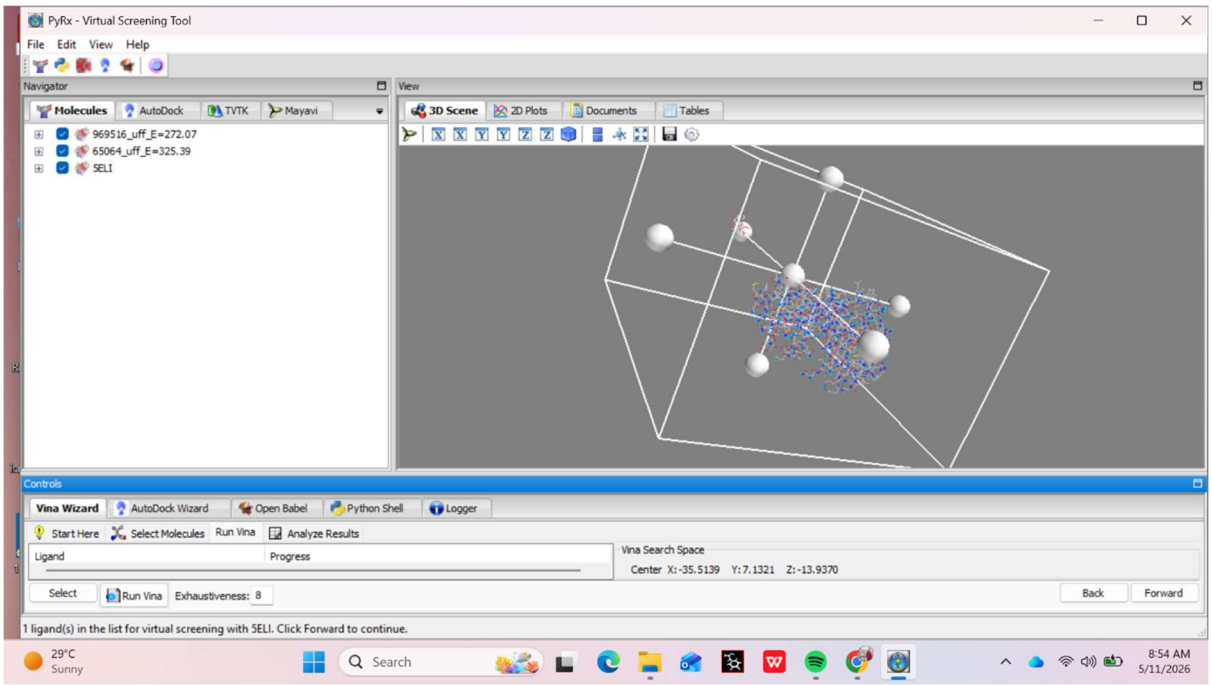


Fig 3.9: Screenshot showing grid box

4 Defining grid box

• Now click on Vina Wizard and select start option on bottom right corner. Start selecting protein and ligand one by one by pressing shift and control button.

• Click on forward. Grid box appears. Return to the 'Molecules' tab located on the right-hand side. Click the loaded protein's "+" symbol.

• All of the residues in the chain will be visible to you. To choose the binding residues, right-click on the residue and choose Atoms, Display, Label, and Atoms. The atoms will start to show up on the protein. Now make the appropriate adjustments to the grid box so that it contains all of the selected residues. The ligand does not need to be enclosed within the grid box.

5 Running vina for docking

• To adjust the exhaustiveness, simply enter the desired number in the box located in the left bottom corner. Once everything has been adjusted, press the "Forward" button.

• Docking will begin, and the processing will be shown. The bottom panel will display the poses and their binding affinities after the docking process is complete. It will show all poses along with RMSD values. Save your file in excel sheet.

• Now analyze the result and the one ligand which has the highest energy with negative sign is selected. Again, open pyrx tab and click on Auto Dock and select macromolecule and select the ligand with highest binding energy. Now right click and select display then all models of the ligands get displayed and select your desired model and save it in pdb format.

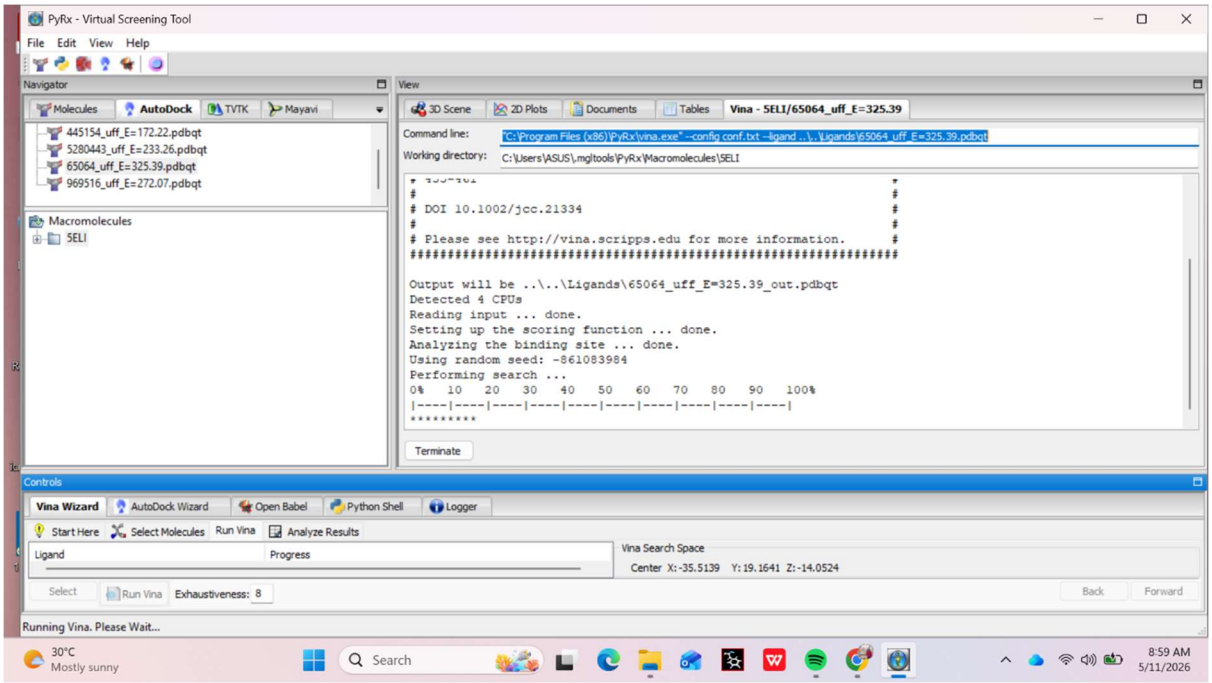


Fig 3.10: Screenshot showing running of vina wizard

6 Open Discovery Studio: -

Start a new project in Discovery Studio.

7 Protein Structure Import:

• Open Discovery Studio and import the structure of the target protein.

• Choose your protein structure file (such as *.pdb) by using File > Open.

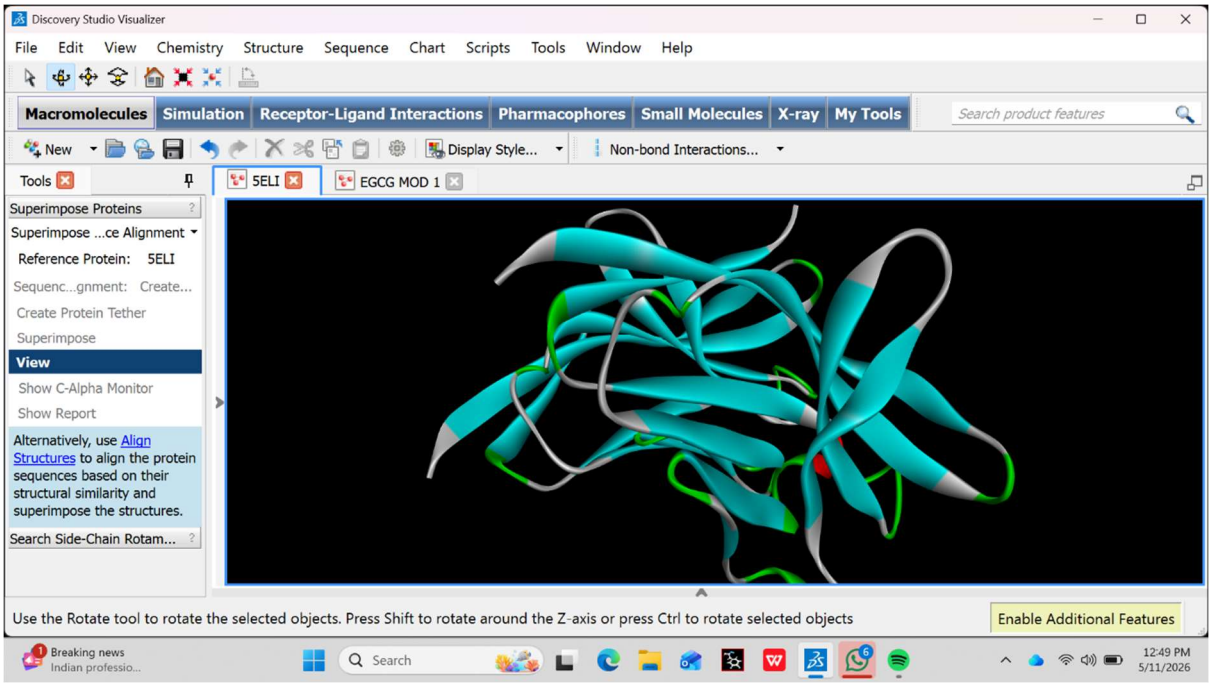


Fig 3.10: Screenshot showing visualization of protein structure in discovery studio

8 Import Docked Ligand Conformations:

• Import the docked ligand conformations.

• Use File > Open and select the converted ligand file (e.g., *.pdb or *.mol2).

9 Visualize Docked Poses:

• Display the protein and ligand together in the 3D workspace.

• Use the View > Sequence panel to ensure the correct structures are loaded.

• Adjust the display settings to show interactions clearly (e.g., stick or surface representations).

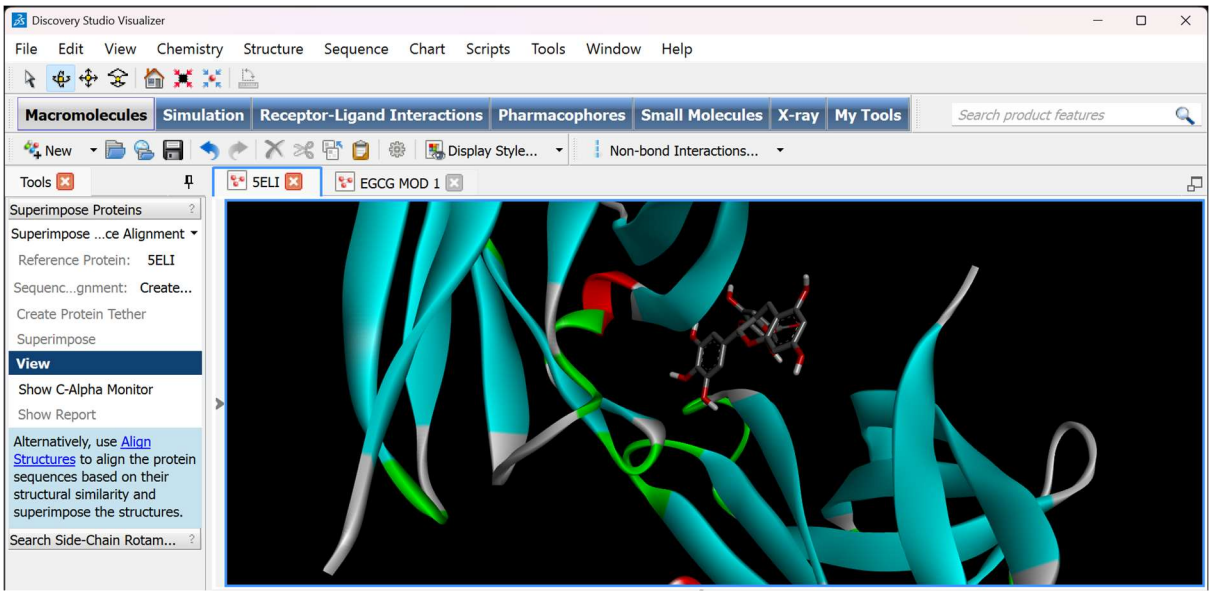


Fig 3.11: Screenshot showing EGCG binding with TREM 2

10 Analyse Binding Affinities:

• Check the binding affinities associated with each docked pose.

• This information can be found in the PyRx log files or the output summary from PyRx.

• Record the binding affinity scores (typically in kcal/mol) for reference.

11 Examine Binding Interactions:

• Use the Analyze > Receptor-Ligand Interactions tool to identify and visualize key interactions between the ligand and the protein.

• Highlight hydrogen bonds, hydrophobic interactions, salt bridges, and π-π stacking interactions. Check for consistency with known binding sites or important residues in the binding pocket.

12 Evaluate Docked Poses:

• Compare multiple docked poses to determine if there is a consensus binding mode.

• Use the View > Compare tool to overlay different conformations and evaluate their similarity.

CHAPTER 4

RESULT

The binding affinities (kcal/mol) between TREM 2 and various natural plant polyphenols are summarized in the table below:

RESULTS

EXCIPIENT	BINDING ENERGY (kcal/mol)
Apigenin	-8.6
EGCG	-8.5
Curcumin	-7.1
Resveratrol	-6.3

Table 1: Binding Energies of TREM2 with selected excipients

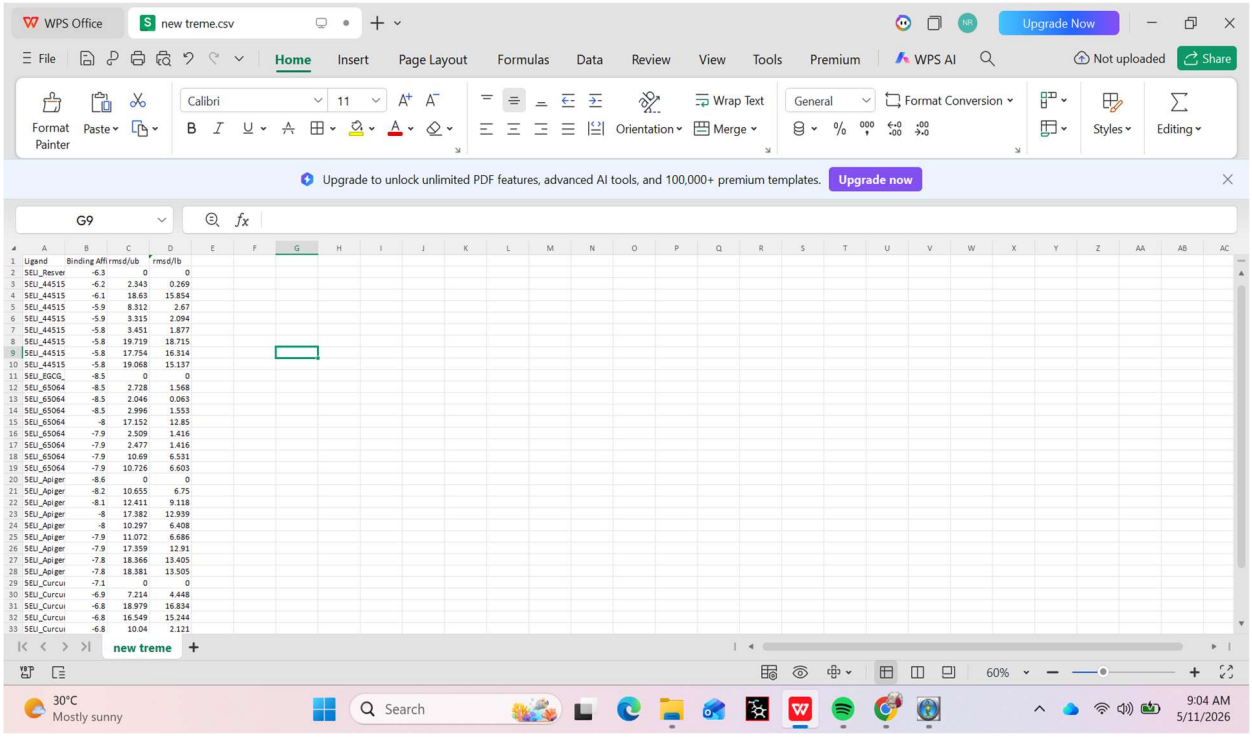


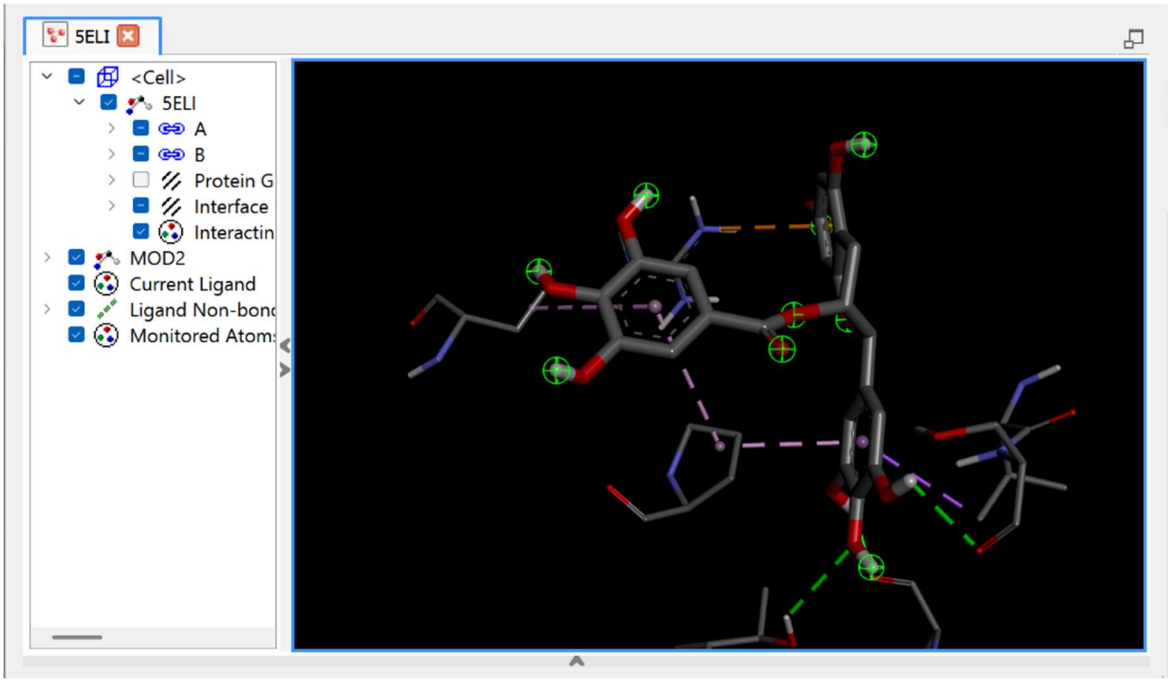
Fig 4.1: Screenshot showing Binding Affinities

These results indicate that Apigenin exhibited the strongest binding to TREM 2, closely followed by EGCG and Curcumin. In contrast, Resveratrol displayed weaker interactions, suggesting a reduced potential for stabilizing the protein.

Molecular docking showed that Apigenin(–8.6kcal/mol), EGCG (–8.5 kcal/mol), and had stronger binding affinities with TREM 2 compared to Curcumin (–7.1kcal/mol) and Resveratrol (–6.3 kcal/mol). Polyphenols formed multiple hydrogen bonds with key TREM 2 residues, suggesting better surface interaction and potential stabilizing effects.

Docking of different excipients with TREM 2

Docking of TREM 2 with EGCG



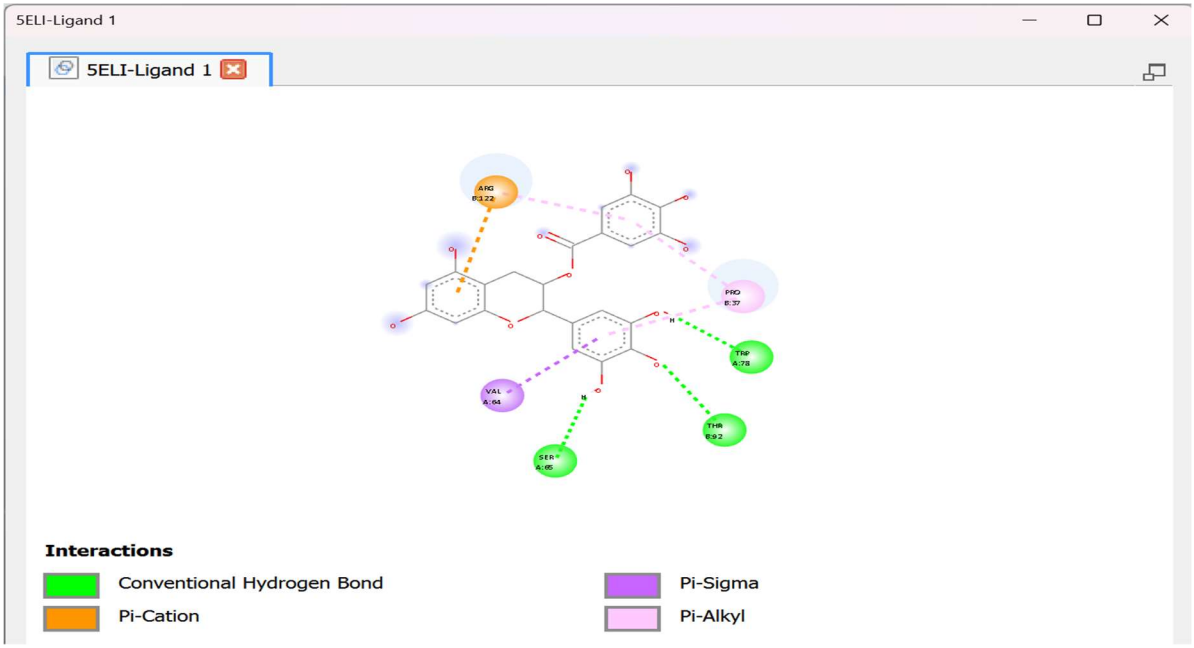
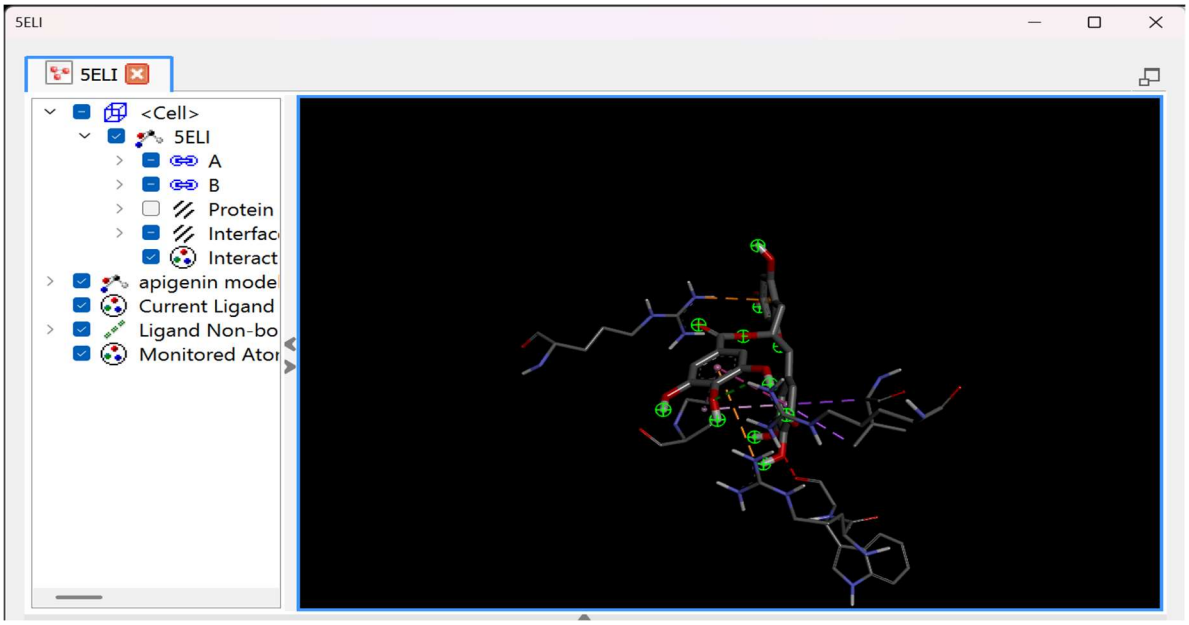


Figure 1: 2D and 3D structures of the TREM2–EGCG complex. EGCG binds with TREM2 through a Pi–Cation bond (ARG122) and a Pi–Sigma interaction (VAL). Several hydrophobic interactions, including Pi–Alkyl interactions (PRO), also contribute to the stabilization of the complex. In addition, conventional hydrogen bonds with THR residues further support the stability of the complex, suggesting a good fit of EGCG within the binding pocket of TREM2.

Docking of TREM 2 with Apigenin



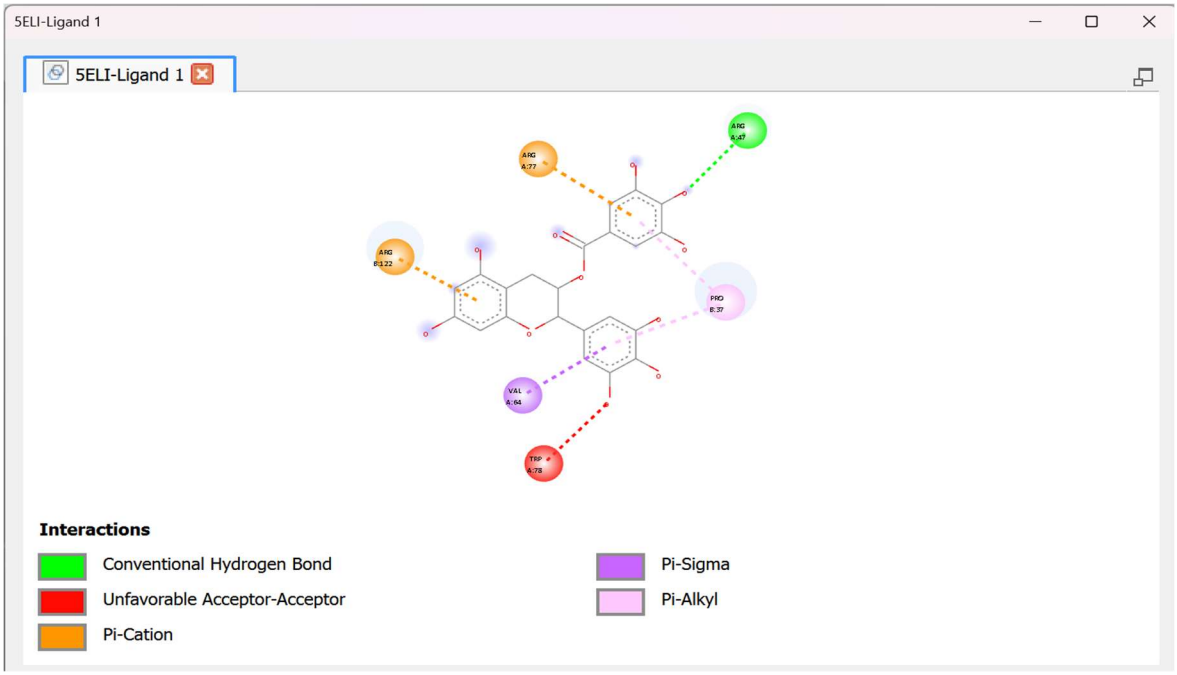
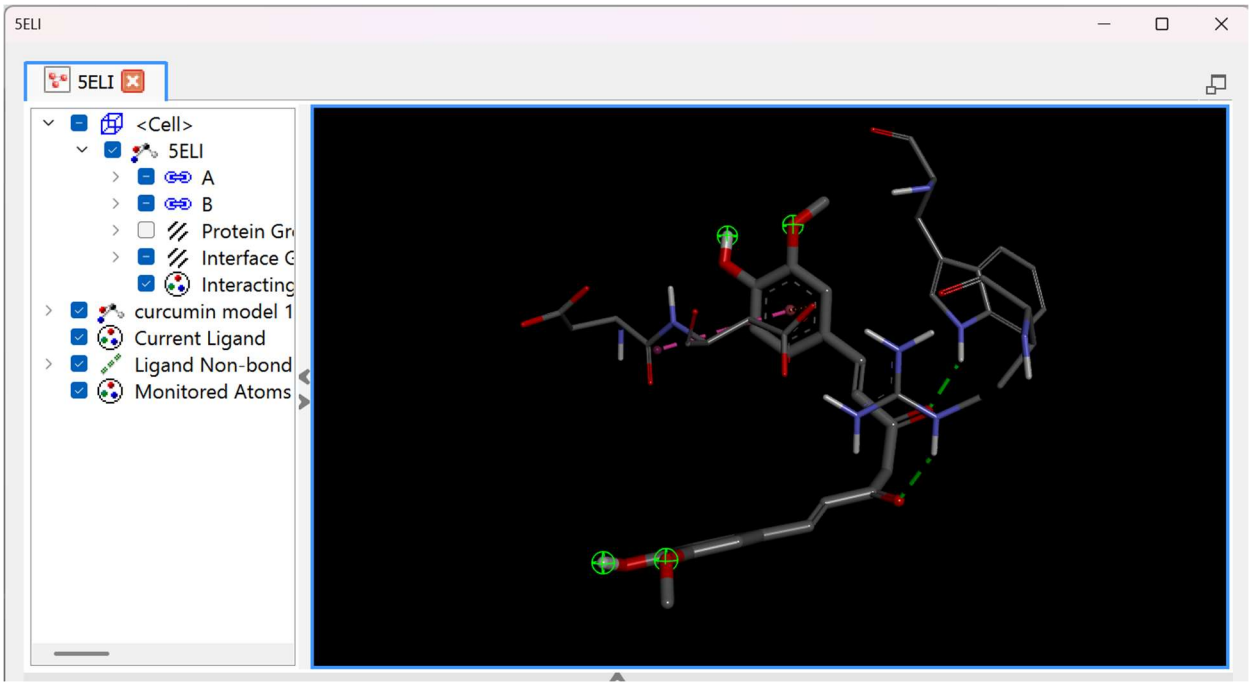


Figure 2: 2D and 3D structures of the TREM2–Apigenin complex. Apigenin interacts with TREM2 through Pi–Cation interactions (ARG47, ARG122) and a Pi–Sigma interaction (VAL64). Several hydrophobic interactions, including Pi–Alkyl interactions (PRO59), also contribute to the stabilization of the complex. A conventional hydrogen bond with ASN residues further supports ligand binding, while an unfavorable acceptor acceptor interaction with TRP residues is also observed. These interactions suggest that Apigenin fits well within the binding pocket of TREM2, contributing to the overall stability of the protein–ligand complex.

Docking of TREM 2 with Curcumin



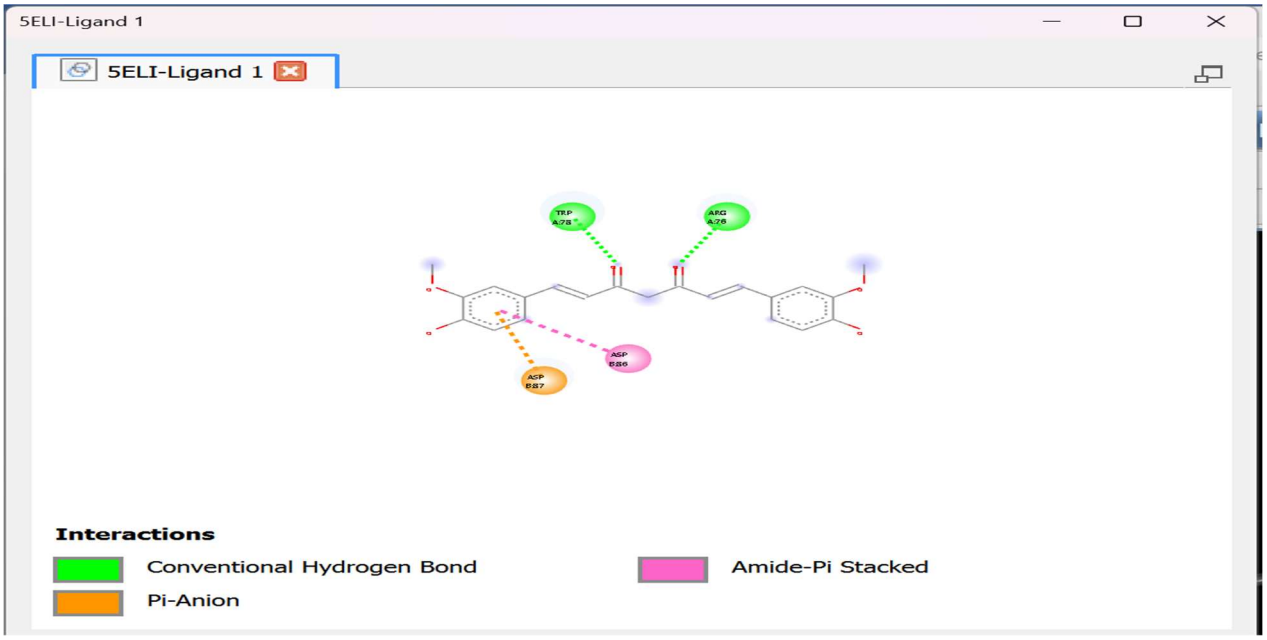
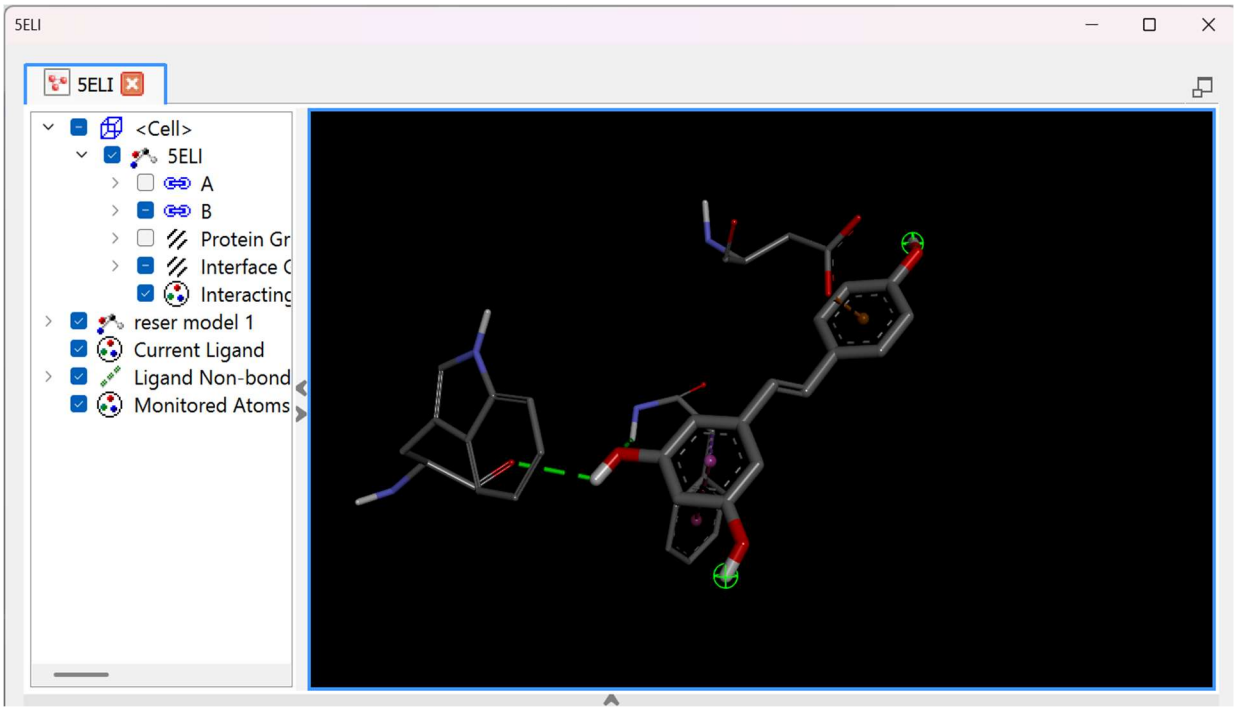


Figure 3: 2D and 3D structures of the TREM2–Curcumin complex. Curcumin interacts with TREM2 through conventional hydrogen bonds (ASN residues), which contribute to stabilizing the ligand within the binding pocket. In addition, a Pi–Anion interaction (ASP) and an Amide–Pi stacked interaction (PRO) are observed, further supporting the stability of the complex. These interactions suggest that Curcumin fits well within the binding pocket of TREM2, contributing to the formation of a stable protein–ligand complex.

Docking of TREM 2 with Resveratrol



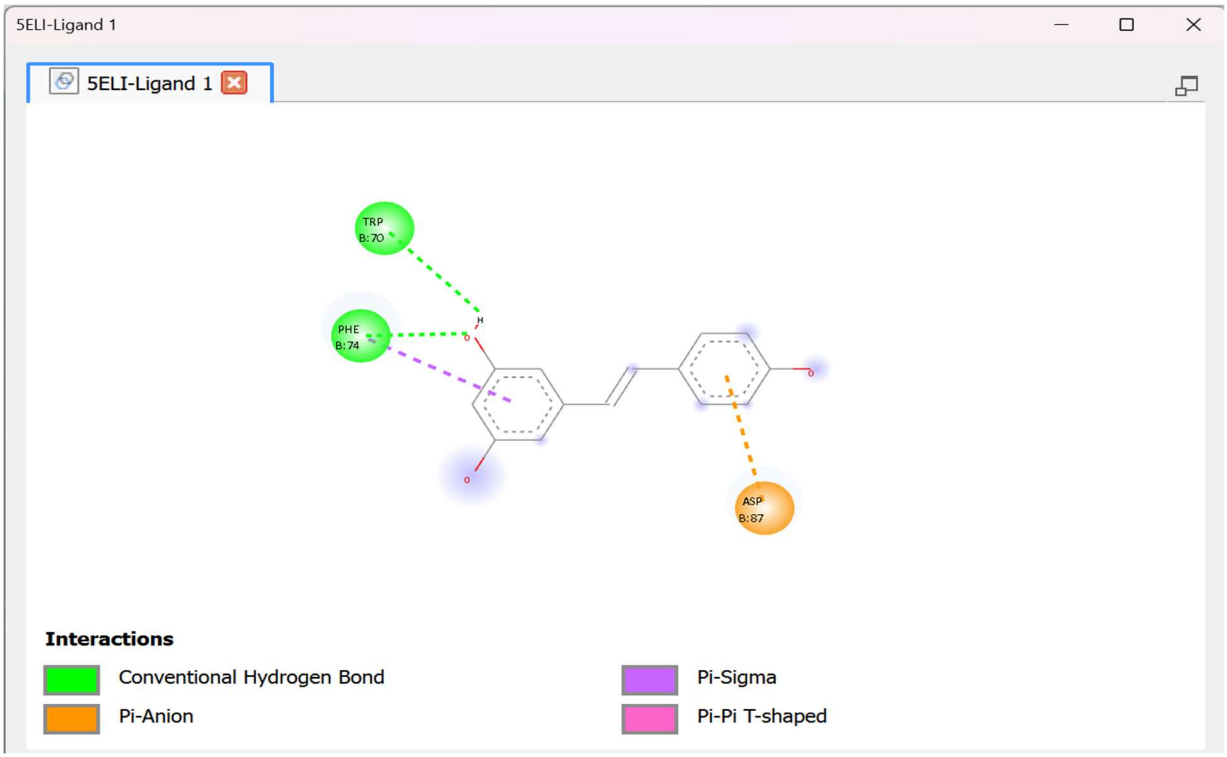


Figure 4: 2D and 3D structures of the TREM2–Resveratrol complex. Resveratrol interacts with TREM2 through conventional hydrogen bonds (TRP and PHE residues), which help stabilize the ligand within the binding pocket. In addition, a Pi–Sigma interaction (PHE) and a Pi–Pi T-shaped interaction further contributes to the stabilization of the complex. A Pi–Anion interaction with ASP is also observed, suggesting that Resveratrol fits well within the binding pocket of TREM2 and forms a stable protein–ligand complex.

CHAPTER 5

DISCUSSION

TREM2 has emerged as a cornerstone in the modern understanding of AD pathogenesis. As a transmembrane glycoprotein primarily expressed on microglia, TREM2 serves as a vital sensor for the brain's microenvironment, orchestrating the transition of microglia into a "disease-associated microglial" (DAM) state. From this study we can reinforce the hypothesis that TREM2 is a crucial microglial receptor involved in regulating neuroinflammation, the phagocytosis of amyloid-β (Aβ), and microglial survival. As reported in literature, impaired TREM2 signaling disrupts microglial activation and reduces the clearance of Aβ plaques, which leads to sustained inflammation and accelerated neurodegeneration. Consequently, targeting this receptor to enhance microglial metabolic fitness and support the transition to protective phenotypes is a significant therapeutic strategy. In the present molecular docking study, the interactions of four natural phytochemicals epigallocatechin gallate (EGCG), apigenin, curcumin, and resveratrol—with the TREM2 receptor (PDB ID: 5ELI) were evaluated. The computational analysis revealed that Apigenin and EGCG exhibited the highest binding affinities, recorded at −8.6 kcal/mol and −8.5 kcal/mol, respectively. These values suggest significantly stronger and more stable interactions within the receptor's binding pocket compared to Curcumin (−7.1 kcal/mol) and Resveratrol (−6.3 kcal/mol). The thermodynamic stability indicated by these binding energies suggests that Apigenin and EGCG possess the requisite structural complementarity to effectively associate with the V-set immunoglobulin domain of TREM2, which is critical for ligand recognition and subsequent immune signaling. The selection of these specific ligands was predicated on their well-documented cytoprotective, anti-inflammatory, and neurorestorative properties. Recent evidence suggests that polyphenolic compounds can modulate neuroinflammatory pathways and attenuate amyloid associated toxicity in various AD models. Our docking results provide a specific mechanistic layer to these general neuroprotective effects, suggesting that Apigenin and EGCG may exert them benefits, at least in part, by directly interacting with TREM2-associated pathways. Such interactions could potentially influence microglial functions relevant to AD pathology, such as increasing the rate of Aβ clearance and controlling chronic neuroinflammation. Although these findings are based on in silico computational analysis, they provide a robust mechanistic rationale for prioritizing Apigenin and EGCG for further experimental validation. From the high binding affinity and stability we get from doing this study suggest these compounds are promising candidates for therapeutic modulation of TREM2 activity. Overall, this experiment supports the potential of natural phytochemicals as effective modulators of microglial receptors and highlights the importance of molecular docking as a preliminary screening approach for identifying candidate compounds capable of altering the progression of Alzheimer's Disease.