RESEARCH ARTICLE

# Docking Study of Selected Phytoconstituents with Acetylcholine Esterase and BChE for its Anti-alzheimers Activity

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**ABSTRACT**

In this research, we have observed known constituents from different plants and perform docking of these phytoconstituents with different AChE & BChE PDBs. It found good binding with Different PDBs. For the docking study, we selected 11 PDBs which include 4TPK, 4AQD, 6EP4, 1H22, 4EY5, 2XQF, 6O4X, 6O4W, 4BDT, 6EQQ, 1B41. Selected phytoconstituents was Sabinene (A), α-Pinene (B), 1,8-Cineole (C), Tras-sabinene hydrate (D), α-Terpineol (E), α- terpentyl acetate (F), Methyl Eugenol (G). We have compared the binding energy and number of hydrogen bonds with Galanthamine. Constituents C and G found good anti-alzheimers activity, and D and E have excellent activity with all PDBs.

**Keywords:** AChE, Alzheimer's disease, BChE, Docking, Herbal, PDBs.

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## INTRODUCTION

Alzheimer's disease (AD), one of the most common neurodegenerative illnesses that commonly culminate in dementia and affects middle-aged individuals, affects one in four people over the age of 85.[1] AD is a progressive condition, meaning that dementia worsens over time. There are now an estimated 46.8 million people living with it globally, according to the King's College London-led World Alzheimer Report 2015, and the incidence of depression is expected to roughly double every 20 years, reaching 74.7 million by 2030 and 131.5 million by 2050. US (4.2 million), China (9.5 million), Brazil (1.6 million), Japan (3.1 million), Germany (1.6 million), Indonesia (1.2 million), India (4.1 million), Russia (1.3 million), Italy (1.2 million), and France (1.2 million) are among the 10 nations that had more than one million dementia patients in 2015. As a result, we and our future generations will bear heavier financial responsibilities because of this predicament. Effective treatments and preventative strategies need to be implemented immediately to address this issue.[1]

The whole of AD or any other kind of dementia cannot be cured by any of these medications or therapies. The medications, however, are made specifically to treat AD and may momentarily lessen symptoms or slow the illness's progression. U.S. Memantine and two anti-cholinesterase inhibitors have received FDA approval for use. More study on AD has been conducted in the last ten years, with an emphasis on the processes of oxidative stress and its significance in pathogenesis. The negative effects of net oxygen radicals include high-quality carbonyl-modified neurofilament protein, glycation, lipid peroxidation adduction products, nitration, and free carbonyls cause damage to AD. It is crucial to remember that this harm affects all neurons at risk of dying from AD, not just those with neurofibrillary tangles.[2]

In the shape of vegetables, bark, leaves, fruits, nuts, and other biodiversity, nature has provided us with various natural treatments. These natural products' nutrients are crucial for preventing and treating many neurodegenerative illnesses, including parkinson's disease, AD, and other neuronal disorders. According to prior studies, phytochemicals that occur naturally, such as the polyphenolic antioxidants present in herbs, vegetables, fruits, and nuts, can prevent neurodegeneration and enhance memory and cognitive abilities.[2]

In this study, we chose seven naturally occurring components (dangerous structures) of diverse plants based on cellular infiltration data and pharmacokinetics research. Recent studies have demonstrated the extensive range of biological actions that both natural and synthetic chemicals exhibit, including antifungal, anti-malarial, anti-tubercular, antibacterial, anti-inflammatory, and antioxidant activity.[3]

All seven substances in our study have antioxidant characteristics, and it has been demonstrated that using these compounds for therapy is quite successful.

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Their neuroprotective properties may be a strategy to stop the illness from worsening. We thus re-evaluated our genes because oxidative stress, one of the main contributors to the development of Alzheimer's, is linked to the disease. Natural substances with antioxidant structure demonstrate their antioxidant action by scavenging free radicals or by enhancing endogenous antioxidant competence. Some of these chemicals also increase the cell's production of antioxidant endogen molecules by activating the NRF/ARE pathways. So, these chemicals can be partners ready for AD testing by eliminating free radicals.[4]

We also took one cholinesterase inhibitor Galanthamine the most commonly used drug. Alzheimer's, as indicators, are linked above our natural chemistry for studies such as drugs. These medications function by blocking an enzyme called acetylcholinesterase, which lowers the amount of acetylcholine in the brain, enhances the actions of antioxidants, and lessens the stresses associated with oxidative stress. Our study has revealed that our natural substances have also demonstrated promising preventative activity. Some of them have been proven to function significantly better against AD targets than prescription medications. Any combination cannot be categorically referred to as a drug molecule without first being supported by a number of factors, including pharmacokinetic characteristics, ADME structures, and possible toxicity. So, we verified all of our computers using various bioinformatics technologies.[5,6]

To assess our chemicals' effectiveness in the targets' binding environment and explain fundamental chemical processes, molecular studies are performed to establish the connection between ligand/drug and protein at the atomic level.[7] Each of the natural chemicals put into the vessels and all the 11 AD proteins go hand in hand, to determine best binding compound used Autodock 4.2. In addition, these computers can be practical in the recognition, development of novel preventive and therapeutic drugs against AD.[8]

## MATERIALS AND METHOD

### Natural Compounds Selection

Seven natural chemicals have been considered standard compounds mentioned as antioxidants in different fields of data and literature. Everything the chemical composition of compounds is shown in Marvin Sketch (Figures 1 and 2).

### Calculation of Basic Pharmacokinetics Parameters

The computer must pass through many filters to qualify as a unique medication. The majority of chemicals that fail in pre-clinical studies do so because they do not reveal the essential characteristics of therapeutic molecules. At the last treatment success of the drug addict, pharmacokinetics parameters, including absorption, distribution, metabolism, dehydration, and toxicity (ADMET) were crucial in the creation of medication formulation. In order to lower the failure rate of a combination of additional processes in the future, predictions of ADMET structures were developed sooner. Pharmacokinetics features of natural chemicals such as TPSA (above surface polarity), LogP, MW (molecular weight), HBA (number of hydrogen bond recipients), HBD (number of hydrogen bond providers), nrtB (no. circulating bonds), violation (violation of the law of

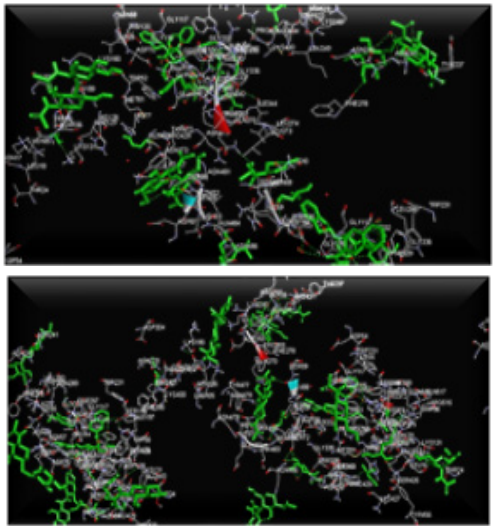

**Figure 1:** Binding of F & G with PDB- 4TPK

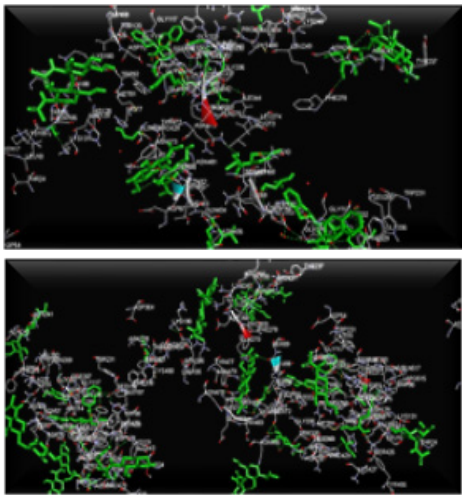

**Figure 2:** Binding of F & G with PDB-4AQD

**Table 1:** Selected Target PDBs

| *S. no* | *PDB ID* | *Protein Name* |
|---|---|---|
| 1 | 4TPK | Butyrylcholinesterase |
| 2 | 4AQD | Butyrylcholinesterase |
| 3 | 6EP4 | Butyrylcholinesterase |
| 4 | 1H22 | Acetylcholinesterase |
| 5 | 4EY5 | Acetylcholinesterase |
| 6 | 2XQF | Butyrylcholinesterase |
| 7 | 6O4X | Acetylcholinesterase |
| 8 | 6O4W | Acetylcholinesterase |
| 9 | 4BDT | Acetylcholinesterase |
| 10 | 6EQQ | Butyrylcholinesterase |
| 11 | 1B41 | Acetylcholinesterase |

Lipinski five) cited by DruLito (Drug LiknessTool) (www.niper.gov.in/pi_dev_tools/DruLiToWeb/DruLiTo_index.html), admetSAR, SwissADMET and the Molinspiration Online tool (http://www.molinspiration.com/).

**Compound Toxicity Prediction**

A crucial step in the creation of medication is combined toxicity. In silico testing can minimize the amount of animal tests in addition to making the toxin quicker. For all of our natural substances, $LD_{50}$ values are thus computed. Values were used to kill 50% of experimental subjects ($LD_{50}$ value) (laboratory mice or other animals). It's the process of calculating the medication and toxicity index. The toxicity of the chemical increases when $LD_{50}$ is decreased. The online calculator ProTox was used to determine these $LD_{50}$ values. Using Discovery Studio 2.5, we also identified its mutagenic, carcinogenic, and skin-irritating characteristics (Acc jewelrys Software Inc., San Diego, CA).

**Molecular Docking**

**Target Preparation**

The full list of Alzheimer's disease-related targets may be found in the Protein Data Bank (PDB) at http://www.rcsb.org/pdb/home/home.do (Table 1). The Swiss PDB viewer tool was used to remove crystallographic water molecules from each target's crystal structure, add any hydrogen atoms that were absent, and lower the power level for all 13 targets.

**Ligand Preparation**

All 7 of the computers' designs were transferred to Marvin Sketch, translated to 3D form, and given chemical geometry at Marvin View. The final step is to save all compounds in PDB configure for future docking investigations.

**Target Ligand Docking**

Docking experiments have revealed crucial details regarding the position of inhibitors in the targeted proteins' binding package.

Throughout the process of cell extraction, all-natural chemicals are trapped in the pit for their proper purposes. Each combination was docked with all targets corresponding to 11 AD, which is why 847 dockings was done (Table 2). This approach can be characterized as the best filter because it uses three levels of selection: first, compounds are included based on their interactions with specific receptors (docking); second, compounds are added on top of that; and finally, RO5 (Lipinski Rule Five) violations and toxins are removed. The PYMOL system of molecular graphics, version 1.7.4.4 (Schrödinger, LLC, Portland OR USA) and Maestro Visualizer (Maestro, Schrödinger, LLC, NY, 2017) were used to show the docking interaction. Autodock 4.2 is used to create docking tutorials. The input function calculates constant inhibition (Ki) of untargeted natural chemicals against Alzheimer-targeted compounds using the following equation:

$$Ki=\exp(\Delta G*1000/RT)$$

Ki=Inhibition constant, ΔG= Docking energy, R= 1.98719 cal $K^{-1}$ $mol^{-1}$, T= 298.15 K

Based on Lipinski's fifth law, the pharmacokinetics of naturally occurring compounds will be regarded as drug addicts. It employs four techniques to assess if a molecule resembles a drug: MW, LogP (logarithm of separation coefficient), 5 or less hydrogen bond donor sites, and 10 or fewer hydrogen bond acceptor sites. It is designed for the majority of oral contraceptive medications.

The bioavailability of molecules that defy these guidelines may be problematic. The entire collection of compounds adhered to Rule 5 well, which contravened Lipinski's law having molecular masses > 500, Log P > 5, and H-bond Donar > 5 >, which might cause an issue with oral bioavailability (Table 3).

TPSA analysis examined present of natural chemical compounds, as Ver's law of good oral discovery, the amount of rotating obligation should ≤ 10, & TPSA ≤ 140A0 values.

**Table 2:** (A-B) Docking Score with Selected Proteins

A

| *PDB* | | | *4TPK* | | *4AQD* | | *6EP4* | | *1H22* | | *4EY5* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Phytoconstituents* | | | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* |
| 1 | Sabinene | A | -4.72 | 2 | -2.21 | 0 | -4.58 | 0 | -4.12 | 0 | -4.94 | 0 |
| 2 | α-Pinene | B | -4.8 | 1 | -1.87 | 0 | -5.09 | 0 | -4.3 | 0 | -5.22 | 0 |
| 3 | 1, 8- Cineole | C | -4.83 | 2 | -1.09 | 0 | -5.11 | 1 | -4.69 | 0 | -5.12 | 0 |
| 4 | Trans- Sabinene Hydrate | D | -4.61 | 3 | -2.04 | 1 | -5.3 | 4 | -4.5 | 0 | -5.33 | 1 |
| 5 | α-Terpineol | E | -4.87 | 1 | 1.08 | 0 | -6.21 | 0 | -4.5 | 6 | -5.25 | 2 |
| 6 | α-Terpentyl acetate | F | -5.42 | 2 | -2.05 | 1 | -6.21 | 3 | -5.18 | 2 | -5.75 | 2 |
| 7 | Methyl Eugenol | G | -4.4 | 3 | -1.87 | 0 | -5.12 | 2 | -4.28 | 1 | -5.9 | 2 |

B

| *2XQF* | | *6O4X* | | *6O4W* | | *4BDT* | | *6EQQ* | | *1B41* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* | *Binding energy* | *H- bond* |
| A -5.03 | 0 | -5.03 | 0 | -4.18 | 0 | -3.89 | 0 | -3.89 | 0 | -4.09 | 0 |
| B -5.4 | 0 | -5.4 | 0 | -4.35 | 0 | -4.28 | 0 | -4.28 | 0 | -4.61 | 0 |
| C -5.33 | 0 | -5.33 | 0 | -4.91 | 2 | -4.43 | 2 | -4.43 | 1 | -4.7 | 1 |
| D -5.31 | 1 | -5.31 | 2 | -4.69 | 7 | -4.17 | 4 | -4.17 | 2 | -4.67 | 7 |
| E -5.46 | 2 | -5.46 | 1 | -5.22 | 5 | -4.17 | 3 | -4.17 | 1 | -4.62 | 8 |
| F -6.18 | 2 | -6.18 | 3 | -5.07 | 5 | -5.21 | 3 | -5.21 | 2 | -5.72 | 5 |
| G -4.89 | 2 | -4.89 | 3 | -4.78 | 5 | -4.55 | 6 | -4.55 | 3 | -4.54 | 6 |

**Table 3:** Shows drug likeness of compounds and violation of Lipinski's rule

| *S. no.* | *Ligand* | *Molecular Formula* | *Molecular Weight (g/mol)* | *logP* | *H-Bond Acceptors* | *H-Bond Donors* | *TPSA* | *% ABS* | *nRB* | *N Atom* | *n Violation* | *%BBB* | $LD_{50}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Sabinene | $C_{10}H_{16}$ | 136.23 | 3 | 0 | 0 | 0 | 109 | 1 | 26 | 1 | 95.54 | 5000 |
| 2 | Alpha-pinene | $C_{10}H_{16}$ | 136.23 | 3 | 0 | 0 | 0 | 109 | 0 | 26 | 1 | 89.59 | 3700 |
| 3 | Eucalyptol | $C_{10}H_{18}O$ | 154.25 | 2.74 | 1 | 0 | 9.23 | 105.91 | 0 | 29 | 0 | 98.86 | 2480 |
| 4 | Trans-sabinene hydrate | $C_{10}H_{18}O$ | 154.25 | 2.19 | 1 | 1 | 20.23 | 102.23 | 1 | 29 | 0 | 97.06 | 2000 |
| 5 | Alpha- tepineol | $C_{10}H_{18}O$ | 154.25 | 2.5 | 1 | 1 | 20.23 | 102.23 | 1 | 29 | 1 | 95.68 | 2830 |
| 6 | Alpha-terpentyl acetate | $C_{12}H_{20}O_2$ | 196.29 | 3.07 | 22 | 0 | 26.3 | 100.20 | 3 | 34 | 0 | 94.29 | 4800 |
| 7 | Methyl Eugenol | $C_{11}H_{14}O_2$ | 178.23 | 2.43 | 16 | 0 | 18.46 | 102.82 | 4 | 27 | 0 | 96.45 | 810 |
| Reference | | | | | | | | | | | | | |
| 1 | Galanthamine | $C_{17}H_{21}NO_3$ | 287.35 | 1.79 | 25 | 1 | 41.93 | 94.975 | 1 | 42 | 0 | 99.59 | 85 |

The number of circulating bonds have been exposed as an excellent indicator of oral drug discovery. It has been found that it is better to discriminate between chemicals with oral drug availability. Any single bond attached to a light atom that is not a ring and rotates is known as a revolving bond (i.e., non-hydrogen). Since amide C-N bonds have a large rotational power barrier, they are not taken into account. All of our compounds' rotating bond numbers have been proven to be appropriate, with values more than 10nRB. Once TPSA was computed, it was discovered that no chemical had a TPSA ≤ 140Å value, thus we used the Zhao *et al.*[9] methods to determine the absorption% of all 7 compounds.

Absorption% (% ABS)= [109- (0.3345* TPSA)

Based on the above formula, we calculate the percentage of our chemical absorption and index values. None of the above chemicals have a negative percentage of absorbance.

TPSA- Topological Polar Surface Area, nAtom- No. of Atoms, %ABS- Percentage of Absorption, nrtB- Number of rotable Atoms, nViolation- Violation of Lipinski's rule, XlogP ≤ 5 H-BD < 5, H-BA < 10, MW < 500.

Drug profiles natural chemicals show promise as a computer prediction of dangerous drugs. For the prediction of $LD_{50}$ for novel compounds, online curriculum PROTOX is employed. The majority of the substances in our investigation were found to be non-toxic (beyond 1000 mg/kg). Conditions of carcinogenicity, mutagenicity, hepatoxicity, and oral toxicity were cited and discovered to be compounds of no compounds as mutagenic, carcinogenic, or heptatoxic, and 2 compounds showing weak and 5 compounds showing mild oral toxicity of these compounds can cause serious skin irritation issues (Table 4).

### Molecular Docking Studies

All the compounds show good activity against all selected PDBs. Among these 7 selected from this Constituents, C and G found good anti-alzhimers activity, and D and E have excellent activity with all PDBs. All of these findings point to the possibility that our natural molecules may interfere with Alzheimer's-related objectives, which calls for additional investigation into our chemical defenses against the illness *in-vivo*.

## DISCUSSION

Natural goods are widely known as a source of medicines for several human maladies and have been utilized since ancient times. These plants' and herbs' therapeutic benefits have sparked research into natural products as possible sources of pharmacological compounds; nonetheless, evolution has produced drug-like molecules, which continue to be the best source of medications and drug recommendations. In our investigation, we chose 7 habitats where the chemicals mostly function by establishing potent free radicals and have considerable antioxidant qualities. Important information that points to an elevated amount of oxidative stress in the AD condition's brain has been gathered recently. It is possible that this contributes to the pathophysiology of neuronal damage and death.10 As a result, combating and preventing oxidative stress might be seen as a key battle in the research and development of anti-drugs. As a result, therapy with these antioxidants can stop or slow the development of AD. These organic substances could seem to be anti-new Alzheimer's. The work was carried out in-silico using various computation techniques based on chemo-informatics or bioinformatics to leverage all chemical

**Table 4:** Shows toxicity of compounds and various toxicities

| *S. no.* | *Compound* | *Carcino-genicity* | *Mutag-enicity* | *Hepato toxicity* | *Oral toxicity* | *Biode-gradability* |
|---|---|---|---|---|---|---|
| 1 | Sabinene | - | - | - | Weak | - |
| 2 | Alpha-pinene | - | - | - | Mild | + |
| 3 | Eucalyptol | - | - | - | Mild | - |
| 4 | Trans-sabinene hydrate | - | - | - | Mild | - |
| 5 | Alpha- tepineol | - | - | - | Weak | + |
| 6 | Alpha-terpentyl acetate | - | - | - | Mild | + |
| 7 | Methyl Eugenol | - | - | - | Mild | + |
| Reference | | | | | | |
| 1 | Galanthamine | - | - | - | Weak | + |

attributes to act as a medication. Predictions for drug-like materials revealed that most compounds adhere to Lipinski's fifth rule and ADMET. As we approach the port, it becomes clear that research also claims that the combinations exhibit a high correlation with objectives related to AD. Given that this is an insilico research, it is important to consider the intricate metabolic changes that occur throughout Alzheimer's. One of the concerns taken into account is how different connections to a complicated system may affect the interaction parameter. These findings point to the existence of a distinct class of anti-disease Alzheimer's medicines that target ligands without just antioxidant action but also preventative and neuroprotective properties. Most of our substances with non-toxic toxins, neuroprotective characteristics, ADMET, RO5, inhibitory barriers, binding joints, antioxidants, and strong communication with Alzheimer's related objectives, as per chemical and pharmacokinetics studies. Thus, our result point to natural substances that could obstruct Alzheimer's-related objectives, which should spur additional research to identify our method's Alzheimer's disease-fighting in vivo substances. Therefore, we suggest further *in-vivo* research and potential clinical trials.

## CONCLUSION

A variety of natural products are used alone or in combination with other neuroprotective medicines, according to various experimental studies, to improve memory and comprehension in AD patients. Overall, this pioneering study was utilized to examine for the first time if compounds derived from natural products could be able to reveal the chemical binding mechanism. The standard case study research was also employed to assess the longest ligands. To understand how the medicine interacts with the symbolic macromolecule (11 AD target), it is crucial to understand the binding capacity of the drug interactions. More research is needed to determine the precise effects of these ecological combinations on various signature approaches, how they operate in various brain areas, their capacity to traverse the blood-brain barrier, and how antioxidant agents interact with their targets. The development of new computers based on natural templates or the application of unique chemical and medical engineering brings up new opportunities for the use of natural anti-AD treatments.

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