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**Research Article**

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# Potential inhibitors against acetylcholinesterase and glutathione S-transferase associated with alzheimer's disease

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**ABSTRACT**

*Cholinesterase inhibitors are employed as the standard therapeutic approach for the treatment of Alzheimer's disease (AD). Cheminformatics tools such as CORINA, Yet Another Scientific Artificial Reality Application (YASARA), JME molecular editor and molecular docking program are employed to determine the binding affinity and mechanism of interaction between the ChE-Is with the target proteins. This approach helps to understand the selectivity of the given drug molecule in the treatment of Alzheimer's disease. The molecular structures of natural products exhibiting GST and AchE inhibitory activities, from medicinally important plants are used for research.*

**Keywords:** Alzheimer's disease(AD), Acetylcholinesterase (AchE), Cholinesterase inhibitors (ChE-Is), Molecular Docking, Glutathione *S*-transferase (GST).

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## INTRODUCTION

Alzheimer disease is the most common form of dementia..During early stages, the most common symptom is difficulty in remembering recent events. When AD is suspected, the diagnosis is usually confirmed with tests that evaluate behaviour and thinking abilities, often followed by a brain scan. In the advance stages, symptoms can include confusion, irritability, aggression, trouble with language, and long-term memory loss[1]. As the sufferer declines, they often withdraw from family and society.[2].The mechanism behind the progression of Alzheimer's disease are not well understood. As per the research, the disease is associated with plaques and tangles in the brain.

The present study aims to design potential AchE and GST inhibitors with structure based drug design. The calculation of free binding energies for several molecules to the same receptor plays a key role in drug designing purposes and obtaining a better understanding of the molecular interactions of proteins with small compounds. This facilitates reliable prediction of the molecule's affinity for its target to guide in the synthesis of potentially new drugs.

## EXPERIMENTAL SECTION

*A. Data Mining*

The three dimensional structure of AchE and GST were obtained from the Protein Data Bank (PDB ID-1ACJ,4IS0). We selected 6 molecules/inhibitors- PrionisideB, Caesaldekarin, Artoninse, Buxapapillinine, Buxaquamarine, Irehine isolated from Barleria prionitis, Caesalpinia bonduc L., Artocarpus nobilis, Buxus Hyrcana plants respectively for our investigation. Structural formulas for all the selected drug molecules are given in Fig.1. The SMILES strings were generated using JME molecular editor[3] and submitted to CORINA[4] for constructing the 3D structure of molecule.

*B. Target Structure Minimization*

Energy minimization for 3D structures was performed by using YASARA tool[5]. It relies on molecular dynamics simulations of models in explicit solvent, utilizing a new partly knowledge-based all atom force field obtained from Amber, possibly with minimum damage done to protein crystal structures by optimizing its parameters.

*C. Computation of docking score between the inhibitor and acetylcholinesterase*

Molecular docking server was used to compute the free energy of binding (ΔG) of docked complexes. 3D coordinates of the AchE and the inhibitor was submitted in PDB format with default parameters. Nonpolar hydrogen atoms were merged and rotatable bonds were defined. Solvation parameters, essential hydrogen atoms, Kollman united atom type charges were added with the help of AutoDock tools[6]. Solis & Wets local search method and Lamarckian genetic algorithm (LGA) were used to carry out Docking simulations [7]. All docking experiments were derived from 10 different runs and terminated after a maximum of 250000 energy evaluations.

## RESULTS AND DISCUSSION

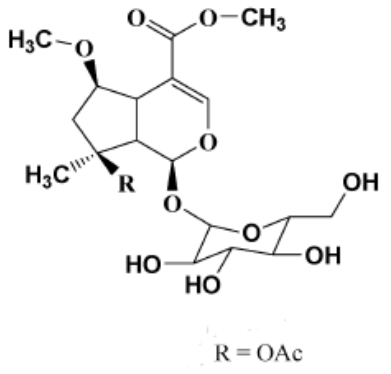
*A. Energy Minimization*

The energy minimization was performed by YASARA program. Higher the total energy, less stable is the protein structure. The total energy of the structure showed that original structure is little higher in energy there by means that structure is unstable. To depict the *in vivo* interaction, we have minimized the energy of the target protein before performing the docking operations. The total energy for the given tructure before and after minimization was found to be -68943.6kJ/mol and −146323.9 kJ/mol for AchE,as well as 634385.1 kJ/mol and -288719.2 kJ/mol for GST respectively (Fig.2). It shows that the minimized structure is more stable than the original one. Thus we hope that our results may exactly correlate with *in vivo* situations.

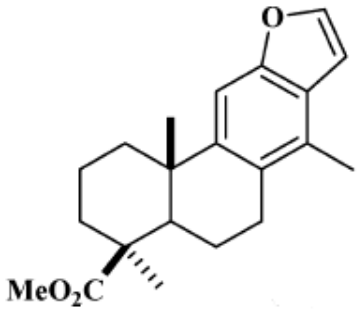
*B. Docking studies of AchE with inhibitor*

Our investigation showed the behavior of protein–ligand complex(Fig.3) of AchE with ChE-Is. The estimated free energy of binding (ΔG) for the target molecule, AchE with Prioniside B,Caesaldekarin, Artoninse, Buxapapillinine, Buxaquamarine, Irehine were found to be -4.2, -10.39, -5.25, 141.61, 24.17 and 2.80kcal/mol respectively (Table 1). The Buxapapillinine, Buxaquamarine, Irehine shows positive ΔG value there by means that binding was not favoured energetically. It is also observed that Caesaldekarin have the better binding affinity with AchE than the other drug molecules. The gradual decrease in ΔG from Caesaldekarin to Buxapapillinine may be attributed to the intermolecular interaction energy between the AchE and drug molecule. The number of intermolecular interactions in the docked complexes are shown in Table 2. It shows that the number of intermolecular interaction is higher in the case of Caesaldekarin compared with other drug molecules.This may lead to the efficient binding of Caesaldekarin with AchE. Since the binding affinity is higher, the value of inhibition constant was very less for the same than the other drug molecules.However, for GST molecule only Prioniside B interacts with negative ΔG of -0.26kcal/mol.

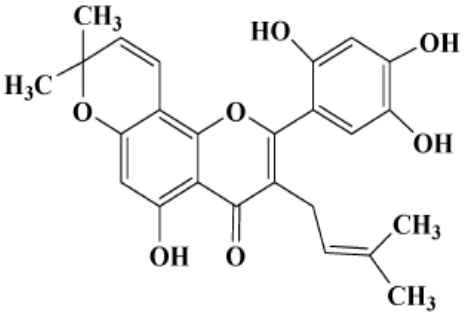
**Fig.1 Two dimensional structures of selected drug molecules**



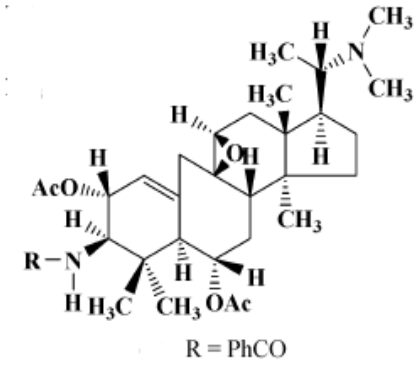

**Prioniside B**



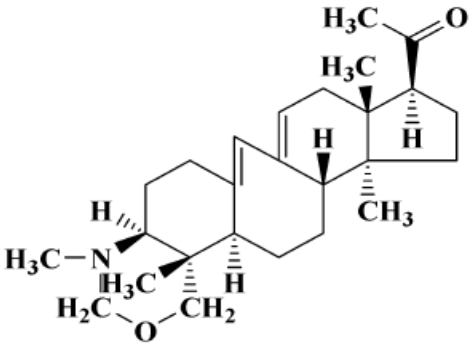
**Caesaldekarin**



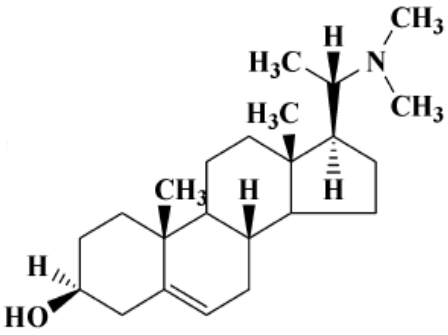
**Artoninse**




**Buxapapillinine**



**Buxaquamarine**




**Irehine**

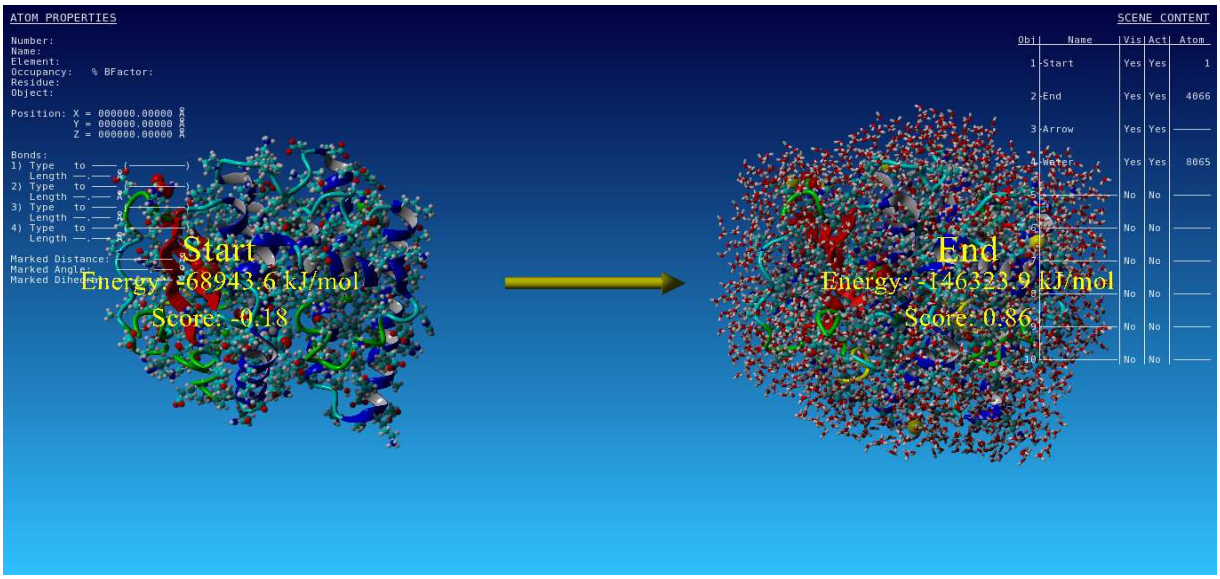



**Fig.2a. Three dimensional structure of AchE before and after minimization with energy values**

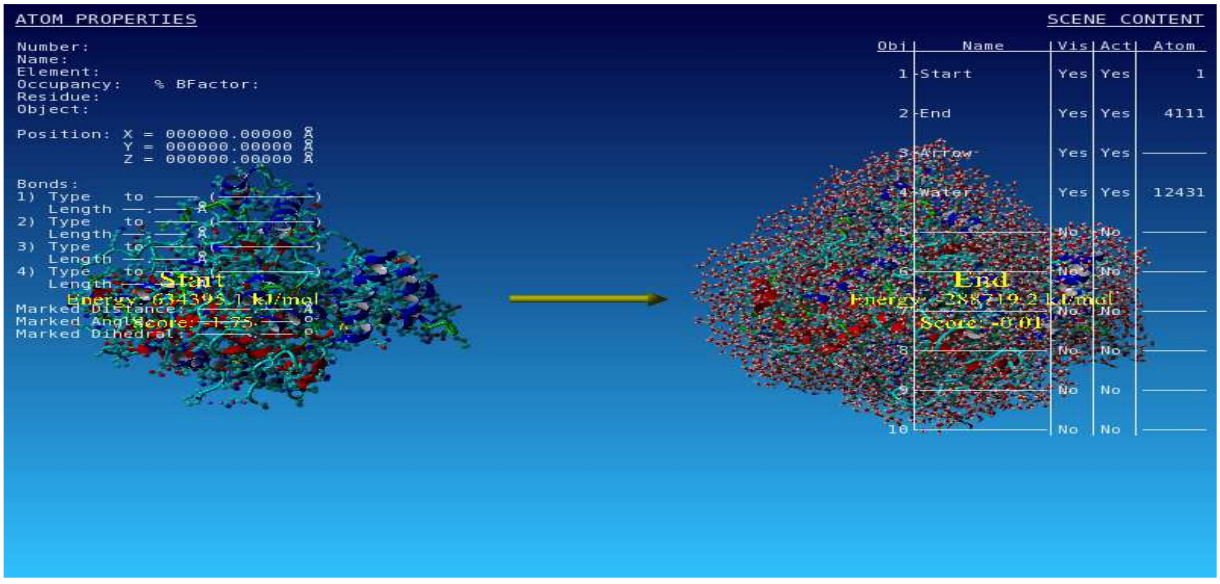


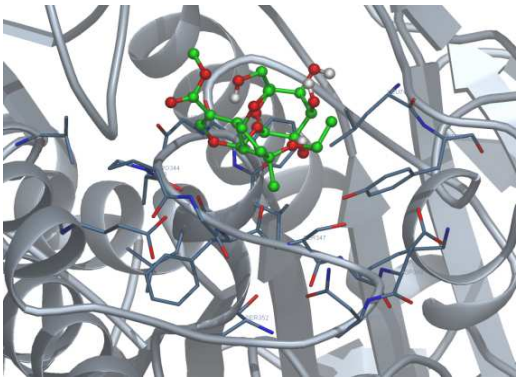

**Fig.2b. Three dimensional structure of GST before and after minimization with energy values**

**Table 1 Docking analysis with selected drug molecules**

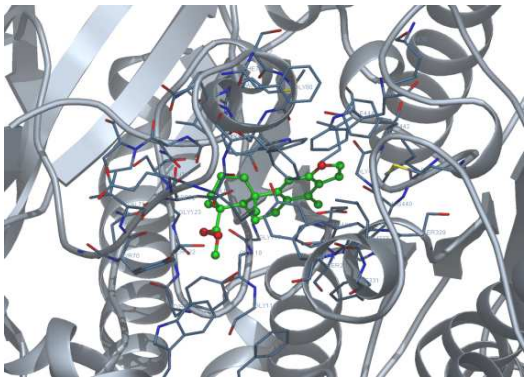
| Drug (Ligand) molecule | Receptor molecule | Estimated free energy of binding (ΔG) kcal/mol | Estimated inhibition constant mM | Total intermolecular interaction energy kcal/mol |
|---|---|---|---|---|
| Prioniside B | AchE | -4.2 | 830.48 | -4.17 |
| Caesaldekarin | AchE | -10.39 | 24.07nM | -11.22 |
| Artoninse | AchE | -5.25 | 141.99 | -8.63 |
| Buxapapillinine | AchE | 141.61 | - | 133.89 |
| Buxaquamarine | AchE | 24.17 | - | 23.87 |
| Irehine | AchE | 2.80 | - | 0.87 |
| Prioniside B | GST | 0.26 | 650.04 | 0.00 |
| Caesaldekarin | GST | 0.65 | - | 0.00 |
| Artoninse | GST | 0.04 | - | 0.00 |

**Table 2 Details of intermolecular interactions in the binding sites of docked complexes**

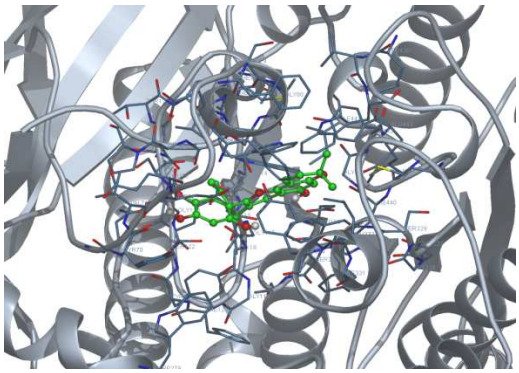
| Complex name | Number of Hbond | Number of polar interactions | Number of hydrophobic interactions | Number of π-π interactions interactions | Number of Cation-π interactions | Other weak forces | Total number of interactions |
|---|---|---|---|---|---|---|---|
| AchE-Prioniside B | 0 | 0 | 1 | 0 | 0 | 3 | 4 |
| AchE- Caesaldekarin | 0 | 4 | 14 | 12 | 0 | 16 | 46 |
| AchE -Artoninse | 2 | 6 | 9 | 10 | 5 | 13 | 45 |
| AchE- Buxapapillinine | 7 | 3 | 10 | 3 | 0 | 9 | 32 |
| AchE -Buxaquamarine | 2 | 4 | 11 | 0 | 1 | 9 | 27 |
| AchE -Irehine | 1 | 2 | 8 | 0 | 2 | 11 | 24 |



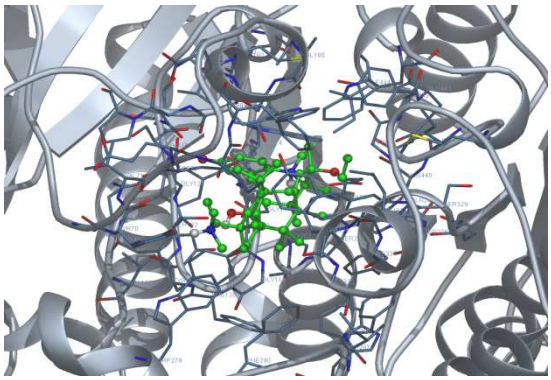
**Prioniside B-AchE complex**



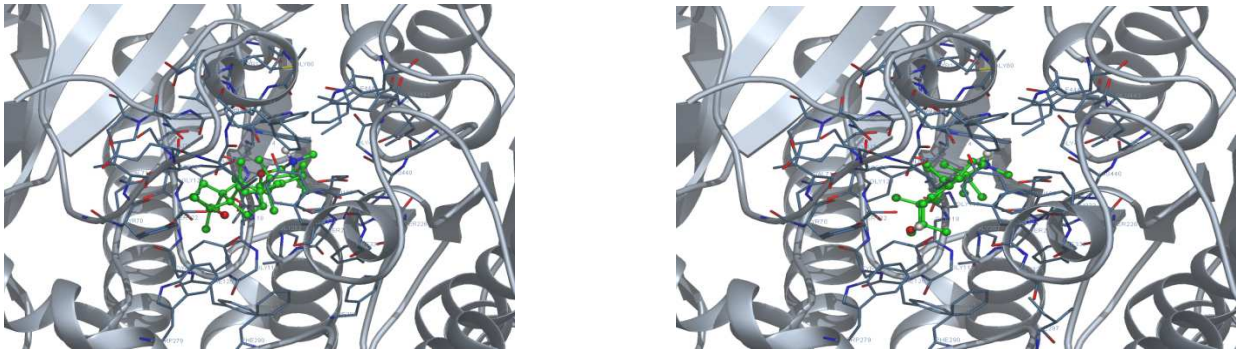
**Caesaldekarin-AchE complex**



**Artoninse- AchE complex**



**Buxapapillinine- AchE complex**



**Buxaquamarine--AchE complex** **Irehine-AchE complex**

**Fig.3 Three-Dimensional view of docked complexes generated using Molecular Docking Server**

## CONCLUSION

We have used computational approach to understand the mechanism of interactions and binding affinity between AchE/GST with drug molecules. The present analysis allows us to draw the number of conclusions. The computational methods such as YASARA are the potential tool for the analysis of catalytic site of the given AchE. The molecular docking program[8]-[14] is helpful in understanding the interaction between the AchE with various drug/lead molecules. Our analysis also shows that Prioniside B, Caesaldekarin, Artoninse could be the potential lead molecule for the inhibition[15] of AchE whereas for GST inhibition Prioniside B would be a better choice. Hence Prioniside B could be used as the template for designing therapeutic lead molecule. The computational efforts discussed above serve well for the future prospects of finding new inhibitors that would contribute to massive reductions in therapeutics development time.

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