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In silico Docking Studies between Atorvastatin and Human Cholesteryl Ester Transfer Protein (CETP) Facilitating the Conversion of Triglycerides Found in VLDL into Cholesterol Esters Found in HDL of *Pan troglodytes*

R.Sathya [a++] and Thirumagal .J [a#*]

[a] Department of Biochemistry, K.M.G. College of Arts and Science, Gudiyatham, 635803, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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[++] *Research Scholar;*
[#] *Assistant Professor & H.O.D;*
**Corresponding author: Email: thirumagaljai12@gmail.com;*

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ABSTRACT

The focus of the current human genomics research is Pan triglodytes, the animal with the highest sequence homology to Homo sapiens. Our research investigation focuses on the Pan triglodytes gene because of this. A plasma protein called cholesterol ester transfer protein (CETP) helps to change the triglycerides present in very low density lipoprotein (VLDL) into the cholesterol esters present in high-density lipoprotein (HDL). Several investigations have shown that CETP is the direct cause of atherosclerosis. Using 3D *In silico* drug docking techniques, we alter the putatively altered target protein CETP and examine its interactions with atorvastatin. To carry out drug docking techniques, the translated amino acid sequence and three-dimensional chemical compound were obtained from the NCBI database. Advanced 3D molecular imaging capabilities were used in post-docking experiments. The results of the docking study made it abundantly evident that atorvastatin directly decreases amino acid mutational sites. Using ideas from molecular dynamics techniques, the electrostatic interaction between atorvastatin and CETP is depicted in three dimensions. Lastly, we can state that atorvastatin, an anti-cholesterol medication, helps to prevent heart attacks and other cardiovascular illnesses. Our goal is to provide an illustration of the molecular mechanism that atorvastatin uses to interact with CETP. Pharmacological research investigations in humans can be conducted by analysing the interaction of Pan triglodytes with CETP and correlating it with human atherosclerosis.

Keywords: Cholesterol Ester Transfer Protein (CETP); atorvastatin; drug docking.

1. INTRODUCTION

Since chimpanzees (*Pan troglodytes*) are the closest extant cousins of humans, they provide the most relevant direct comparison for attempting to understand the evolution of the human brain. Focusing on the distinctions between chimpanzee and human brain connectivity can offer important insights into the particular evolutionary alterations that may have happened along the human lineage (Wang et al., 2024). Cardiovascular disease (CVD) is the world's leading cause of death, accounting for about 20 million deaths in 2021 (Vaduganathan et al., 2022). Therefore, large-scale epidemiological studies are needed to study secular patterns in CVDs in order to focus future preventative efforts, determine the focus of future therapy trials, and emphasize the resources needed in healthcare to tackle expanding problems. Vast efforts have already been made in this direction, as evidenced by the Global Burden of Diseases study and the major medical associations' statistics on CVD. Unfortunately, trustworthy age-standardized incidence rates, statistics on changes over time, and information on how these vary by population subgroups are still lacking for all CVDs (Roth et al., 2020; Tsao et al., 2023; Timmis et al., 2022). CETP expression and plasma activity may have an impact on atherosclerosis, and how well these factors work will likely depend largely on the metabolic and genetic settings (Nandanpawar et al., 2023). Most human and rabbit studies indicate that CETP expression or activity promotes atherosclerosis development, mostly through increasing non-HDL lipoprotein levels and decreasing HDL cholesterol plasma levels. Nonetheless, experimental data, primarily from genetically modified mice, supports the notion that CETP may prevent atherosclerosis when the LDL receptor function is preserved (Oliveira & Raposo, 2020). One noteworthy novel function of CETP that may be related to atherogenesis is its possible modulatory influence on inflammation. Mice that express CETP all over their body are resistant to death in sepsis scenarios (Suganya & Devi, 2023).

Additionally, a link has been seen between the survival probability of patients with sepsis and the plasma CETP content. But according to recent research, the results for humans and animals differed (Trinder et al., 2019; Trinder et al., 2021). These differences are understandable given the difficulty in differentiating the effects of reciprocal changes in HDL and CETP concentrations on both protection against acute inflammation and susceptibility to it in vivo.

Genetics accounts for approximately half of the variability in an individual's HDL-C level. The cholesterol ester transfer protein (CETP) gene is relevant because, while being the subject of intense debate and discussion, the CETP protein is regarded to be a useful target for interventions for CVD prevention and is implicated in the RCT process (Schmidt et al., 2021). The mechanism

meant to obstruct the RCT process is the exchange of esterified cholesterol for triacylglycerol (TG) from HDL-C to low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) via CETP (Ouimet et al., 2019). One method to enhance HDL-C levels and perhaps improve CVR is to inhibit CETP. According to Nurmohamed et al. (2022), human CETP inhibition increases cholesterol concentrations in potentially protective HDL subfractions while decreasing them in harmful non-HDL subfractions.

According to data from the World Health Organization (WHO), cardiovascular disease (CVD) accounted for 32% of all deaths globally in 2019 (Generoso et al., 2019). This makes CVD the top cause of mortality. 38.1% of adult Americans, or 93.9 million people, had total cholesterol levels that were either equal to or higher than 200 mg/dL, according to data collected between 2015 and 2018 (Tsao et al., 2022). Furthermore, elevated levels of low-density lipoprotein cholesterol were linked to 4.51 million deaths worldwide in 2020—a 19% increase from 2010. Increases in low-density lipoprotein (LDL) lead to atherosclerosis, a condition where excessive cholesterol accumulates in arteries throughout the body. A myocardial infarction or stroke is more likely when low-density lipoprotein (LDL) builds up in the coronary and carotid arteries.

Because *Pan troglodytes* and Homo sapiens are orthologous species, there is a similarity in the amino acid sequence homology between the CETP of these two animals and that of humans. The fundamental purpose of this research is to restrict the global spread of atherosclerosis by employing currently existing anti-cholesterol drugs. In this study, we investigate the relationship between the anti-cholesterol drug atorvastatin and the functional domain of cholesterol ester transfer protein (CETP).

2. MATERIALS AND METHODS

Protein Sequence Selection: The proteomics database was used to find the UniProt of A0A2I3TFA7-CETP. In order to conduct molecular drug docking study, atorvastatin (CID: 60823) was received from NCBI- PubChem (https://pubchem.ncbi.nlm.nih.gov)11. Three-dimensional structures were predicted using Discovery Studio Software, a potent molecular visualization software. Molecular Drug Docking and 3D Interactions: Studies on molecular drug docking have made use of the automated molecular drug docking server HDock (http://hdock.phys.hust.edu.cn/) (Yan et al., 2020). The molecular affinities of atorvastatin and the Cholesterol Ester Transfer Protein (CETP) were determined by use of a 3D Ligand-Protein docking technique. Post-docking research were carried out with the use of the Discovery Studio program. Based on the docking score, a detailed investigation of the 3D image (3D H-bond/Electrostatic interactions) was conducted using the molecular dynamics concept.

3. RESULTS AND DISCUSSION

With a common ancestor that lived between 6 and 8 million years ago, chimpanzees (*Pan troglodytes*) and humans (Homo sapiens) are among the closest surviving primate relatives (Staes et al., 2019). In this docking investigation, atorvastatin and the CETP protein sequence were docked using the HDOCK server. Fig. 1 displays the amino acid composition of both normal and mutant proteins. Its 493 amino acid length is found on a chromosome. In Fig. 2, the 2D and 3D structures of atorvastatin were shown as colored atom models using the software Discovery Studio. In this instance, 3D molecular drug docking investigations are performed using the HDOCK server. Fig. 3 shows the 3D structure of the CETP, which may be viewed in secondary structure color in the Discovery Studio software. The molecular action of CETP facilitates the transfer of neutral lipids, such as triglycerides and cholesteryl ester, between lipoprotein particles. It facilitates the equimolar transport of triglyceride from VLDL to HDL and the net migration of cholesteryl ester from high density lipoproteins/HDL to triglyceride-rich very low density lipoproteins/VLDL (Piko et al., 2023). Three different studies (Liao et al., 2021; Piko et al., 2023; 2020) discussed how CETP affects the molecular function and characterizations of the gene. Additionally, our study is based on earlier work that reviews the state-of-the-art for inslico docking investigations.

Atorvastatin (Lipitor®) is one medication in the statin class that lowers cholesterol. By preventing the liver's natural production of cholesterol, statins reduce abnormal levels of cholesterol and lipids, which lowers the risk of cardiovascular disease. More precisely, the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) Reductase, which catalyzes the conversion of HMG-CoA to mevalonic acid, is competitively

blocked by statin medications. Many molecules involved in lipid metabolism and transport are produced by this important metabolic activity, including low-density lipoprotein (LDL), sometimes known as "bad cholesterol," very-low-density lipoprotein (VLDL), and cholesterol. [PubChem CID: 60823]

The HDOCK server, a vital part of the HDOCK system, provides a cutting-edge platform for biological data inclusion, homology search, macromolecular docking, accurate and speedy protein-protein docking, and template-based modeling. The server uses a hybrid algorithm that combines template-free and template-based docking to automatically anticipate the interaction between the molecules when data about the receptor and ligand molecules is entered.

The ability to accept amino acid sequences as input and the hybrid docking strategy of the HDOCK server, which enables the inclusion of experimental data regarding small-angle X-ray scattering and the protein-protein binding site during the docking and post-docking processes, are two characteristics that distinguish it from other similar docking servers. A number of previous studies (Jaiswal et al., 2021; Liu et al., 2022; Lopez et al., 2019; Maithreyee & Prabha, 2023; Nijanthi & Munivelan, 2023; Yang et al., 2022; Zashumo et al., 2022; Grace et al., 2022; Zashumo et al., 2023). The interactions between atorvastatin and the CETP protein at different binding amino acid positions are shown in Figs. 2 through 6. Figures show the drug-receptor complex view and related drug binding scores for CETP and atorvastatin: The drug binding affinity with the highest value is 5 -7. -184.90 kcal/mol. Interestingly, we found that the domain portions of the Protein kinase C phosphorylation site [456-459] PS00006 CK2_PHOSPHO_SITE Casein kinase II phosphorylation site (Bruserud & Reikvam, 2023; Tovell & Newton, 2023) are directly bound by our selected atorvastatin. The interactions depicted in Figs. 8 and 9 between the H Bond and the amino acids support the conclusive findings of the post-3D docking investigations. Features of intramolecular binding consist of the following. The following amino acids' interactions with H bonds: (ARG:218,VAL:215,ALA:219,VLA:215,GLY:279, ASP:459,PHE:488,LEU:484).

MLAATVLTLALLGNAHACSKGTSHEAGIVCRITKPALLVLNQETAKVIQTAFQRASYPDITGEKAMMLL
GQVKYGLHNIQISHLSIASSQVELLEAKSIDVSIQNVSVVFKGTLKYGYTTAWWLGIDQSIDFEIDSAIDL
QINTQLTCDSGRVRTDAPDCYLSFHKLLLHLQGEREPGWIKQLFTNFISFTLKLVLKGQICKEINVISNI
MADFVQTRAASILSDGDIGVDISLTGDPVITASYLESHHKGHFIYKNVSEDLPLPTFSPALLGDSRMLYF
WFSERVFHSLAKVAFQDGRLMLSLMGDEFKAVLETWGFNTNQEIFQEVVGGFPSQAQVTVHCLKMP
KISCQDKGVVVNSSVMVKFLFPRPDQQHSVAYTFEEDIVTTIQASYSKKKLFLSLLDFQITPKTVSNLT
ESSSESIQSFLQSMITTVGIPEVMSRLEVVFTALMNSKGLSLFDIINPEIITRDGFLLLQMDFGFPEHLLV
DFLQSLS

Fig. 1. *Cholesterol Ester Transfer Protein* (CETP) amino acid sequence of *Pan triglodytes*

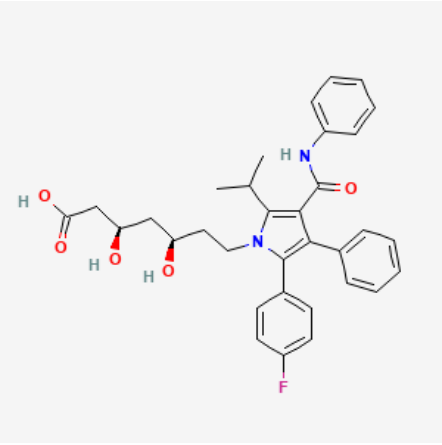


Fig. 2. Using Discovery Studio software, the 2D structure of atorvastatin can be examined, along with the correspondingly colored atoms

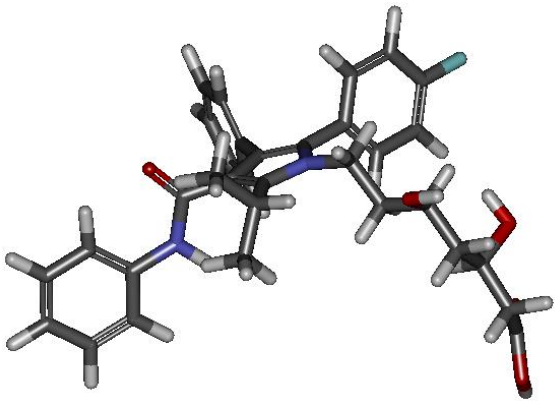


Fig. 3. Using Discovery Studio software, the 3D structure of atorvastatin is displayed, along with the correspondingly colored atoms

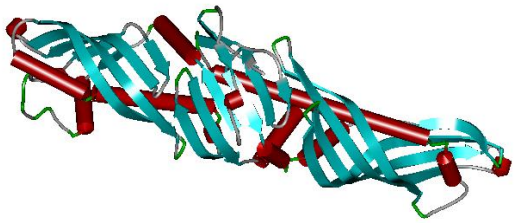
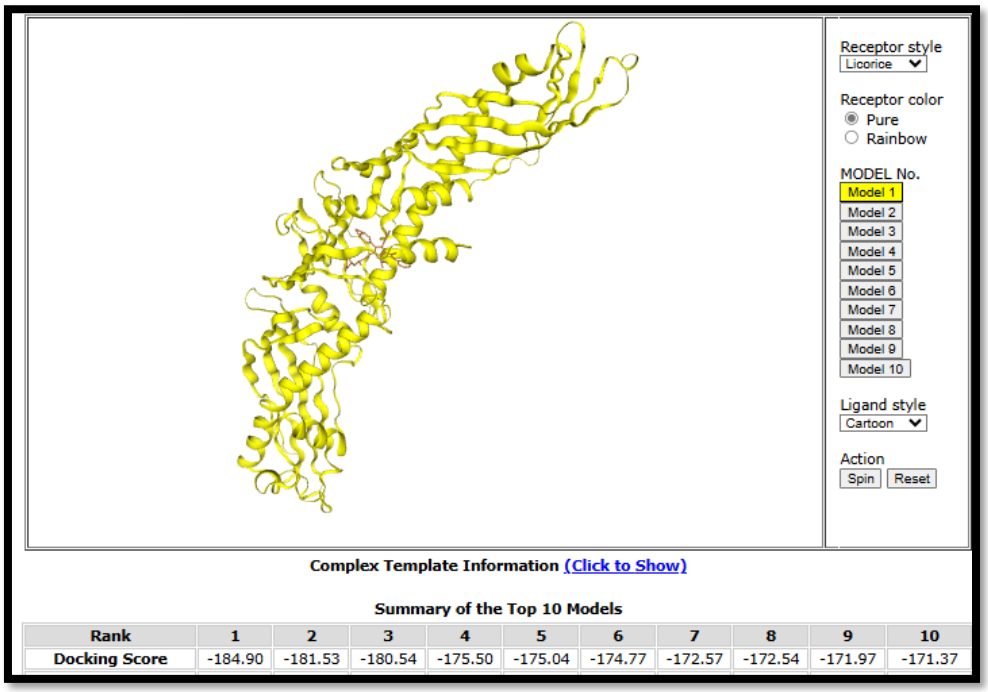


Fig. 4. *Cholesterol Ester Transfer Protein* (CETP) of *Pan triglodytes* in three dimensions as seen with Discovery Studio



Rank	1	2	3	4	5	6	7	8	9	10
Docking Score	-184.90	-181.53	-180.54	-175.50	-175.04	-174.77	-172.57	-172.54	-171.97	-171.37

Fig. 5. Using the H-Dock website, molecular docking studies were conducted on atorvastatin and the *Cholesterol Ester Transfer Protein* (CETP) of *Pan triglodytes*, displaying the corresponding binding scores

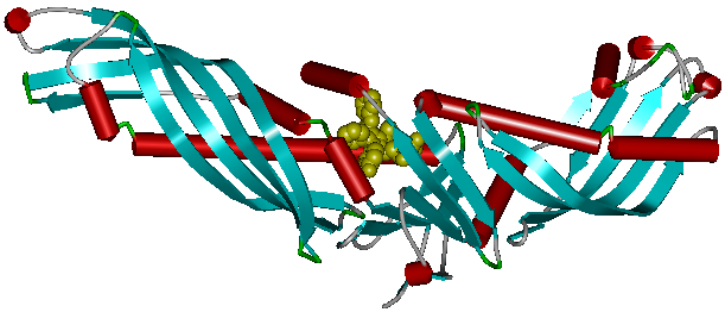


Fig. 6. Using Discovery Studio software, the complex three-dimensional structure of the *Cholesterol Ester Transfer Protein* (CETP) of *Pan triglodytes* with atorvastatin was observed

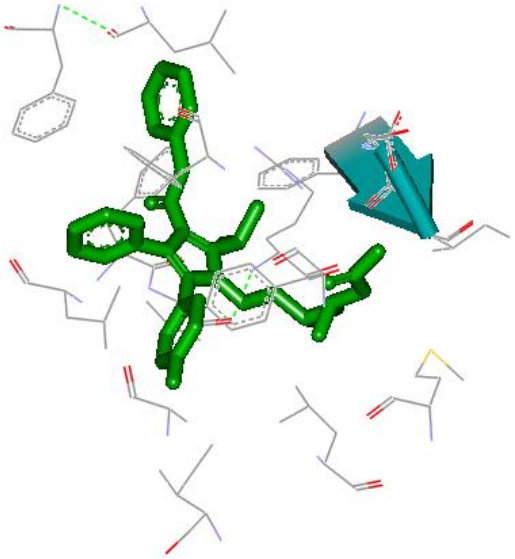


Fig. 7. Using Discovery Studio software, an H-bond interaction between the *Cholesterol Ester Transfer Protein* (CETP) of *Pan triglodytes* and atorvastatin is displayed, revealing the corresponding amino acids

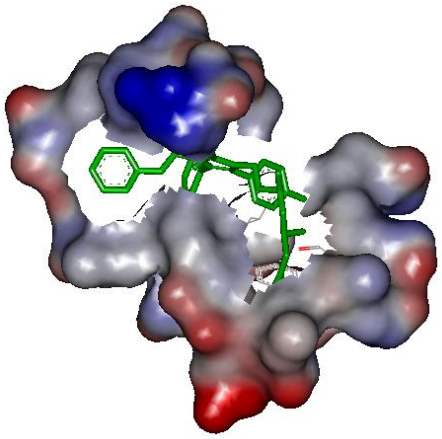


Fig. 8. Using Discovery Studio software, an H-bond interaction between the *Cholesterol Ester Transfer Protein* (CETP) of *Pan triglodytes* and Atorvastatin is shown in surface model view

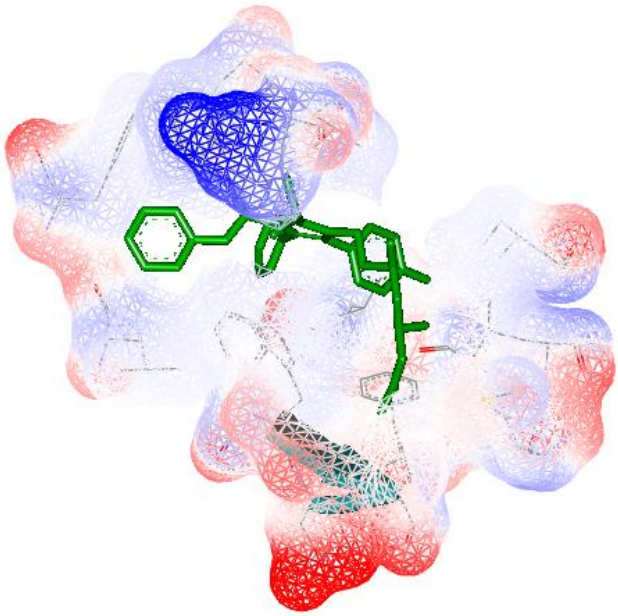


Fig. 9. Using Discovery Studio software, an H-bond interaction between the *Cholesterol Ester Transfer Protein* (CETP) of *Pan triglodytes* and atorvastatin is shown in surface model view

4. CONCLUSION

By directly binding to the mutant area of Pan triglodytes' CETP protein, atorvastatin connects to and inhibits the expression of the protein responsible for atherosclerosis. The binding contact between the CETP protein and atorvastatin provides a good illustration of the 3D H-bond interaction, according to docking scores. Therefore, we draw the conclusion that, despite the fact that atorvastatin is currently prescribed to lower cholesterol, our research suggests that it can also be used to prevent atherosclerosis in humans. Thus, this drug can be used to prevent atherosclerosis as well as several other associated cardiovascular conditions.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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