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In silico Drug Docking Interactions between Kaempferol and Apolipoprotein A-I (APOA1)

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Authors' contributions

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

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ABSTRACT

Apolipoprotein A-I (APOA1) is typically linked to a significant increase in cardiovascular risk and atherosclerosis. Numerous clinico-genetic research have demonstrated this reality. Our work uses 3D Insilico drug docking techniques to make the possible mutant target protein Apolipoprotein A-I (APOA1) interact with kaempferol. One of the main phytochemical components found in *Hibiscus rosa-sinensis* is kaempferol. It has been demonstrated that *Hibiscus rosa-sinensis* has a variety of pharmacological actions that can treat a wide range of human illnesses. We investigate the relationship between kaempferol and APOA1. The use of sophisticated 3D molecular visualization tools was employed in post-docking experiments. Kaempferol directly suppresses amino acid mutational sites, as demonstrated by the docking study results. APOA1 and Kaempferol's molecular 3D H-bond interaction is depicted in 3D view-based notions of molecular dynamics techniques. Finally, we draw the conclusion that kaempferol helps to prevent cardiovascular illnesses.

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Keywords: Apolipoprotein A-I (APOA1); kaempferol; drug docking In silico.

1. INTRODUCTION

Blood apolipoproteins, which make up a significant portion of HDL, include ApoA-I [1]. Apart from its involvement in the reversal of cholesterol, ApoA-I exhibits potent anti-inflammatory properties [2]. With levels down by at least 25% during acute inflammation, it is regarded as an anti-inflammatory protein. In rheumatoid arthritis, Crohn's disease, and other immunological disorders, ApoA-I reduces the inflammatory response by blocking the synthesis of TNF-a and IL-1 [3]. It has also been discovered that there is a negative relationship between ApoA-I levels and pancreatitis severity [4,5,6]. Additionally, in hypertriglyceridemic pancreatitis, our earlier research found a negative association between ApoA-I levels and the severity of the disease [7]. A negative connection has been shown between ApoA-I and the severity of sepsis cases. Furthermore, it has been demonstrated that giving septic rats ApoA-I mimetic peptide increases their survival rates. ApoA-I's anti-inflammatory properties are also critical in preventing atherosclerosis and slowing the formation of tumors (Busnelli M et al., 2024).

A prevalent long-term illness in clinical practice, dyslipidemia is characterized by abnormalities in plasma cholesterol, triglycerides (TGs), or both [8]. In addition, dyslipidemia poses a significant risk for atherosclerotic cardiovascular diseases (ASCVDs), which include peripheral vascular disease, CAD, and stroke. Major risk factors for ASCVD include decreased high-density lipoprotein cholesterol (HDL-C) and increased levels of lipoprotein A, TGs, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) [9]. Dyslipidemia is closely linked to systemic metabolic disorders, such as diabetes and obesity [10,11]. Dyslipidemia causes fat to accumulate intrahepatic, which in turn causes liver fibrosis, non-alcoholic steatohepatitis (NASH), and non-alcoholic fatty liver disease (NAFLD). Furthermore, according to Yang A.L. and McNabb-Baltar J [12] Baass A et al. [13], severe hypertriglyceridemia (HTG) causes serious clinical disorders as acute pancreatitis and familial chylomicronemia syndrome (FCS). Thus, the management of dyslipidemia is crucial for both primary and secondary prevention of lipid diseases [14].

Based on the results of the previous study, phytochemical analysis of extracts from *Hibiscus rosa-sinensis* showed the existence of many substances in different portions of the plant, including tannins, saponins, glycosides, anthocyanins, flavonoids, and several others. Kaempferol is the plant chemical employed in this experiment for docking investigations. One of the main chemical components of Hibiscus rosa is kaemferol [15]. This chemical constituent's pharmacological action has been demonstrated before. Determining the anti-cholesterol effects of kaempferol against the protein target, Apolipoprotein A-I (APOA1), is the primary motivation for the current insilico research. The main issue that those with cardiovascular disease must deal with is that the condition has a severe impact on health, which in turn impacts people's daily lives. Developing a novel treatment drug for different types of Apolipoprotein A-I (APOA1)-related atherosclerosis would be greatly aided by the research we are now conducting.

2. METHODOLOGY

Protein Sequence Selection: The UniProt of (P02647 APOA1_HUMAN) was located using the proteomics database. Kaempferol (CID: 5280863) from NCBI- PubChem (https://pubchem.ncbi.nlm.nih.gov) was used to do molecular drug docking research. A powerful molecular visualization program named Discovery Studio Software was used to predict three-dimensional structures. 3D Ligand and Protein docking and interactions: The automated molecular drug docking server HDock (http://hdock.phys.hust.edu.cn/) has been used in studies on molecular drug docking [12]. Using the 3D Ligand-Protein docking procedure, the molecular affinities of kaempferol and the Apolipoprotein A-I (APOA1) were ascertained. The Discovery Studio program was used to conduct post-docking studies. The molecular dynamics idea was applied to thoroughly examine the 3D image H-Bond interaction (3D Ligand –Protein complex) based on the docking score.

3. RESULTS AND DISCUSSION

The HDOCK server was utilized to dock the APOA1 protein sequence with *Kaempferol* in this docking investigation. Its length is 267 amino acids (aa). Fig. 1 shows the amino acid representations of the normal and mutant forms. Using the Discovery Studio program, the 2D and

3D structures of kaempferol were rendered as atomic color models in Figs 2-3. In this case, the HDOCK server is used to carry out 3D molecular drug docking analyses. *Kaempferol* is a tetrahydroxyflavone in which the four hydroxy groups are situated at positions 3, 5, 7 and 4'. Reducing oxidative stress and acting as an antioxidant, it is currently being investigated as a potential cancer treatment. It functions as a geroprotector, a human urine metabolite, a human blood serum metabolite, a plant metabolite, an antibacterial agent, and a human xenobiotic metabolite. It belongs to the family of flavonols and is a tetrahydroxyflavone and 7-hydroxyflavonol. It is an acid conjugate of an oxoanion *kaempferol*. [CID for PubChem: 5280863].

Natural flavonoids like *kaempferol* have been extracted from plants like delphinium, witch hazel, citrus, and others. The melting point of *kaempferol*, a yellow, crystalline solid, is 276-278 degrees Celsius. It is somewhat soluble in water, and well soluble in hot ethanol and diethyl ether. [E. I. Ulkurnain et al., 2023]. A number of closely related *apolipoprotein* (APO) genes with related roles make up the APOA1/C3/A4/A5 gene cluster on chromosome 11q23.3. These genes are significant modulators of lipoprotein transport and metabolism [16]. Fundamental research and epidemiological investigations consistently show that APOA1/C3/A4/A5 plays a crucial role in intestine, plasma, and hepatic lipid homeostasis.

SNPs in APOA1 have been used extensively recently as predictive markers for CAD risk, and prospective weight reduction studies in obese patients have demonstrated the considerable effects of the APOA1 (rs670) gene on insulin resistance and LDL cholesterol levels. In 2019, Dai W et al. [17] and de Luis D et al. [18].

The APOA1's 3D structure is depicted in Fig. 4, which may be examined in the Discovery Studio software in secondary structure color. An essential component of the HDOCK system, the HDOCK server offers a state-of-the-art platform for biological data inclusion, task management for accurate and timely protein-protein docking, homology search, macromolecular docking, and template-based modeling. When information on the receptor and ligand molecules is entered, the server employs a hybrid algorithm that combines template-free and template-based docking to automatically predict the interaction between the molecules. Two features that set the HDOCK server apart from other similar docking servers are its ability to accept amino acid sequences as input and its hybrid docking strategy, which allows experimental data about the protein-protein binding site and small-angle X-ray scattering to be included during the docking and post-docking processes. Our results are in agreement with a number of earlier studies [19,20,18,21,22,23,24,25,26,27]. Figs 2 through 6 depict the interactions between the APOA1 protein and *kaempferol* at various binding amino acid locations. The drug-receptor complex image and matching drug binding scores for APOA1 and *Kaempferol* are displayed in Figs. 5-7-146.51 *kcal/mol* is the drug binding affinity with the highest score. Interestingly, we found that *Kaempferol* directly interacts at the C-terminal of Lipid-binding serum glycoprotein [245-478] IPR001124 [28]. Figs. 8 and 9, which depict the H Bond's interactions with the previously stated amino acids, clearly highlight the findings of the post-3D docking research [29-31]. The interacting amino acids at the H bonds are as follows:

(LEU:264,SER:252,LYS:250,SER:252,SER:252, VAL:251,ARG:147,GLN:267,AGR:147,GLU:144) [32,33].

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MKAAVLTLAV LFLTGSQARH FWQQDEPPQS PWDRVKDLAT VYVDVLKDSG RDYVSQFEGS
ALGKQLNLKL LDNWDSVTST FSKLREQLGP VTQEFWDNLE KETEGLRQEM SKDLEEVKAK
VQPYLDDFQK KWQEEMELYR QKVEPLRAEL QEGARQKLHE LQEKLSPLGE EMRDRARAHV
DALRTHLAPY SDELRQRLAA RLEALKENGG ARLAEYHAKA TEHLSTLSEK AKPALEDLRQ
GLLPVLESFK VSFLSALEEY TKKLNTQ

MKAAVLTLAV LFLTGSQARH FWQQDEPPQS PWDRVKDLAT VYVDVLKDSG RDYVSQFEGS
TLGKQLNLKL LDNWDSVTST FSKLREQLGP VTQEFWDNLE KETEGLRQEM SKDLEEVKAK
VQPYLDDFQK MWQEEMELYR QKVEPLRAEL QEGARQKLHE LQGKLSPLGE EMRDRARAHV
DALRTHLAPY SDELRQRLAA RLEALKENGG ARLAEYHAKA TEHLSTLSEK AKPALEDLRQ
GLLPVLESFK VSFLSALEEY TKKLNTQ
```

Fig. 1. *Apolipoprotein* A-I (APOA1)'s normal and mutant amino acid sequences are shown, with the corresponding mutated amino acid locations indicated in yellow (A-T : 61) (K-M:131) (E-G:163)

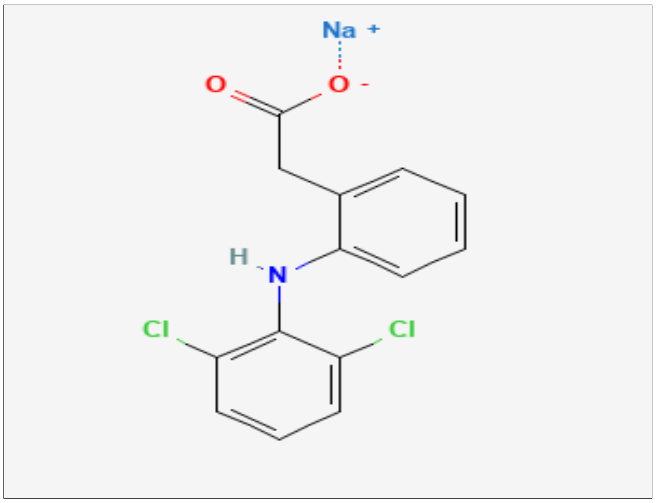


Fig. 2. Discover studio software was used to view the 2D structure of *kaempferol* along with the correspondingly colored atoms

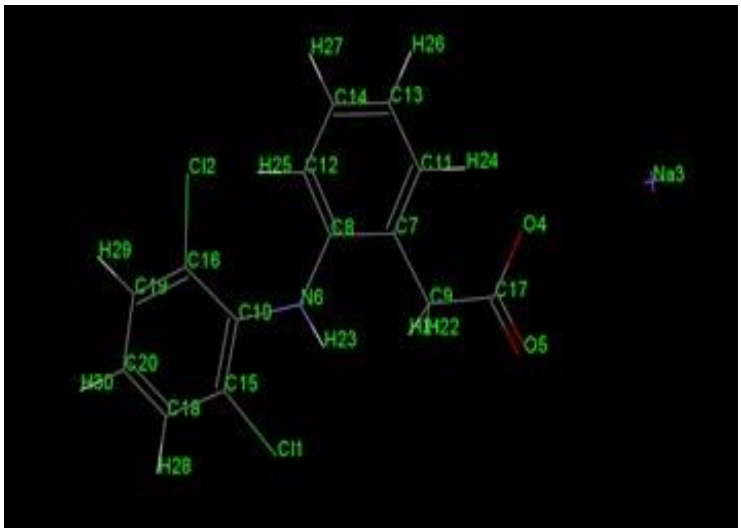


Fig 3. Exploring the *Kaempferol* 3D structure with its correspondingly colored atoms using Discovery Studio software

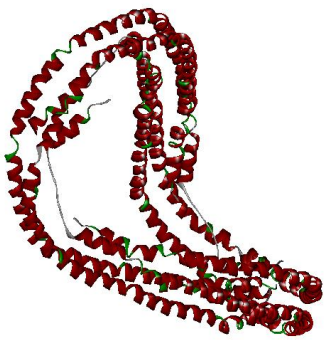
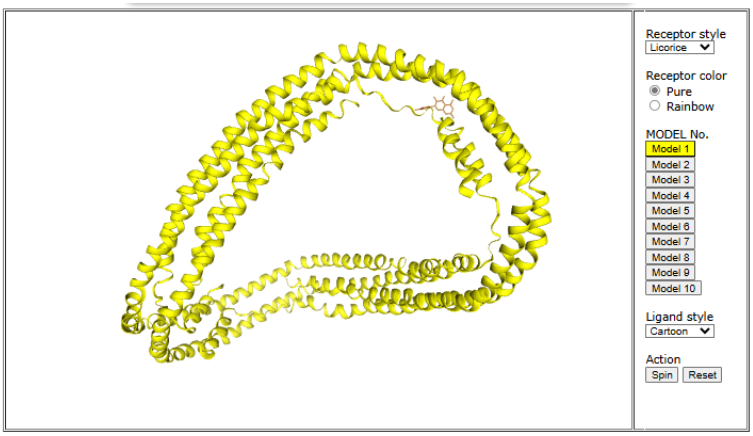


Fig. 4. *Apolipoprotein* A-I (APOA1)'s 3D structure as seen using Discovery Studio



Complex Template Information (Click to Show)

Summary of the Top 10 Models

Rank	1	2	3	4	5	6	7	8	9	10
Docking Score	-146.51	-144.13	-142.97	-141.82	-141.47	-140.33	-140.19	-139.97	-139.72	-139.32

Fig. 5. Using the H-Dock server, molecular docking studies were conducted on *Kaempferol* with *Apolipoprotein* A-I (APOA1), displaying the corresponding binding scores

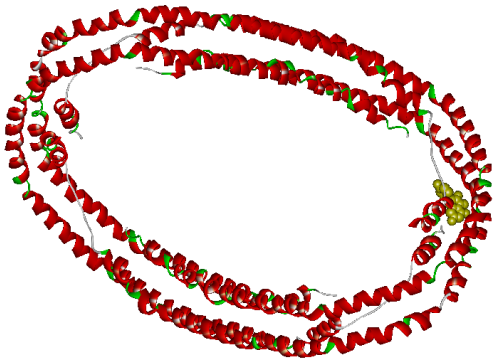


Fig. 6. *Apolipoprotein* A-I (APOA1)'s complex 3D structure with *kaempferol* visualized with Discovery Studio

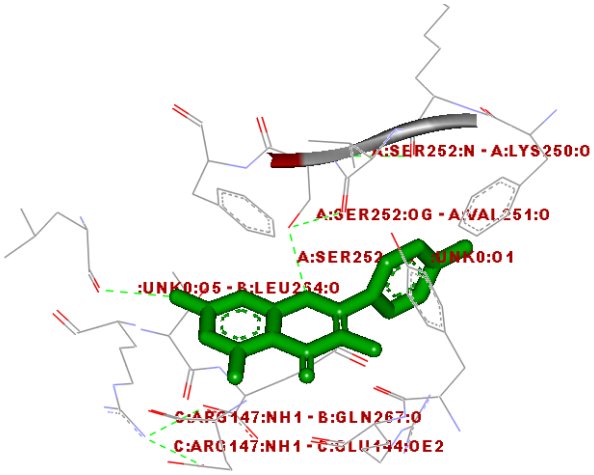


Fig. 7. Using Discovery Studio software, an H-bond interaction between the protein *Apolipoprotein* A-I (APOA1) and *kaempferol* is displayed, along with the corresponding amino acids

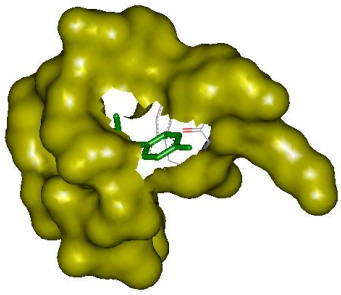


Fig. 8. *Apolipoprotein* A-I (APOA1) and *kaempferol* H-bond interaction in a surface model visualized with Discovery Studio software

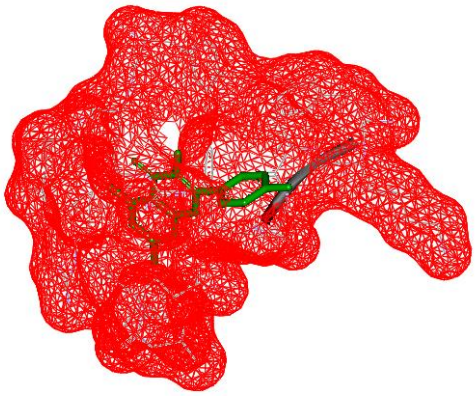


Fig. 9. *Apolipoprotein* A-I (APOA1) protein and *kaempferol* interact through an H-bond in a surface model that may be visualized with Discovery Studio software

4. CONCLUSION

Since *kaempferol* directly binds to the mutant region of the APOA1 protein, it attaches to the protein and reduces its production. Docking scores indicate that the 3D H-bond interaction is well-illustrated by the binding interaction between the APOA1 protein and *kaempferol*. Thus, we draw the conclusion that *kaempferol* has the potential to be an anti-Cholesterol medication that helps treat the consequences of atherosclerosis related cardio vascular disease. The complete Insilico study unequivocally demonstrates that *kaempferol*, an anti-Cholesterol medication, may have pharmacological effects on *Apolipoprotein* A-I (APOA1).

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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