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Research Article

MOLECULAR DOCKING STUDIES ON APIGENIN AS A TARGET WITH MAPK P^{38} FOR CARDIOVASCULAR DISEASES

M. Mahalakshmi, Arjunan Sundaresan, Vadivel Balamurugan*

Department of Biotechnology, Sri Vinayaga College of Arts and Science, Ulundurpet-606 107, Tamil Nadu, India.

***Corresponding author's Email: balakal78@gmail.com**

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ABSTRACT

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels (arteries, capillaries and veins). It is the most serious disease on which extensive research is being done all over the world. Structure based drug designing offers a computational approach to identify the potential leads which can be developed into a drug. The In-Silico study of the current work aimed at inhibiting target MAPK P38 protein. This exhibited a minimal energy against the targets hence suggesting the stability of the compound. Five different forms of apigenin were docked against target, stated that all five is efficient to act on the targets by exhibiting promising interactions and good scores. Especially pure form of apigenin shows very efficient score than others. Since it is from a natural source the compound is nontoxic and has reduced side effects.

Keywords: Cardiovascular disease, Apigenin, In Silico. MAPK P^{38}.

INTRODUCTION

Molecular docking has become an increasingly important tool for drug discovery. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behaviour of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively[1,2].

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels (arteries, capillaries and veins). CVDs and their risk factors are major contributors to global morbidity and mortality[3]. CVD is the leading noncommunicable disease; nearly half of the 36 million deaths due to noncommunicable diseases are caused by CVD[4]. Apigenin [5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one] is a naturally occurring, non-toxic, non-mutagenic phytonutrient flavonoid, commonly present in various fruits and vegetables. Apigenin has long been considered to have various biological activities such as antioxidant[5], anti-inflammatory[6] and anti-tumorigenic effect[7] in various cell types.

Activation of p38 mitogen-activated protein kinase (MAPK P^{38}) plays an important role in apoptotic cell death. The role of MAPK P^{38} in myocardial injury caused by ischemia/reperfusion, an extreme stress to the heart, is

unknown. Ischemia followed by reperfusion further activated MAPK P38, and the maximal level of activation (6.3-fold, P<0.01) was reached 10 minutes after reperfusion. MAPK P38 plays a pivotal role in the signal transduction pathway mediating post-ischemic myocardial apoptosis and inhibiting MAPK P38 may attenuate reperfusion injury. At the molecular level, stimulation of MAPK P38 induces intrinsic myocardial apoptosis activity and cellular signaling that results in reperfusion injury[8].

The main objective of this study is to validate the ethnopharmacological knowledge of apigenin targeted with MAPK P38 by using modern computer aided drug designing tools and to develop safe and more reliable treatment for cardiovascular disease.

MATERIALS AND METHODS

Target Identification: The targets were selected the three dimensional structures of the target protein, mitogen activator protein kinase (figure: 1) MAPK P38 having the resolution of 1.91 A0 was retrieved and has been downloaded from the online protein structure repository, Protein Data Bank (PDB) (www.rcsb.org/pdb). The structures were determined by Xray Diffraction method and had ligands coupled in the binding site. (ID: 4DLI).

Preparation of compounds: The structures of the compounds apigenin and four other derivatives of apigenin were downloaded from Pubchem in SDF format and converted to PDB format using the tool CACTUS SMILES (ONLINE TOOL). The compound structures were energy minimized and considered for docking studies. The original ligands of the targets were also prepared similarly and taken for docking.

Molecular Docking: Graphical-Automatic Drug Design System for Docking, Screening and Post-Analysis program iGEMDOCK was used to gain the docking results of the listed compounds with the target. The binding site of the target was prepared and the energy minimized compounds were imported.

The docking protocol consisted of 25 generations per ligand and the population size of 100 random individuals. All the docking conformations were performed twice using genetic evolutionary algorithm and the fitness of the docked structures were calculated. The hydrophobic preference and electrostatic preference were set to 1.00. The binding site of the target was identified at a distance 8Å. The empirical scoring function of iGEMDOCK was estimated as: Fitness = vdW + Hbond + Elec. Here, the vdW term is van der Waal energy. Hbond and Elect terms are hydrogen bonding energy and electro statistic energy, respectively.

RESULT

The docking studies revealed that the apigenin and its similar compounds were efficient enough to act against the MAPK P38. Five compounds were docked against the target with the crystal structure of the target MAPK P38 and three compounds such as apigenin 4'-O-rhamside, apigenin and 4',7-dimethylapigenin exhibited good hydrogen bond interaction respectively -3.74, -9.92 and -9.35 . They interacted with the binding site residues such as ASN 196, SER 251, ASP292, ASP 294and GLU 192.Result was reported on table 1.

Interaction between apigenin and MAPK P38

Apigenin has an energy level -100K Cal/mol, compare with other compounds it had good interaction with three residues of a target such as SER 251, ASP292 and ASP 294. Its hydrogen bond value is -9.92. Result was shown in figure 1.

Interaction between 4',7-dimethylapigenin and MAPK P38

4',7-Dimethylapigenin has an energy level -102.2 KCal/mol, it also had good interaction with one residue of a target such as GLU 192. Its hydrogen bond value is -9.35. Result was shown in figure 2.

Interaction between apigenin7-O-b-glucuronide and MAPK P38

Apigenin7-O-b-glucuronide has an energy level -104.13 KCal/mol, it had interaction with two residues of a target

Table 1: Binding Energy for the Best Compound Docked Against MAPK P38

Apigenin and its derivatives	Binding energy (k cal/mol)	Vdw	H bond	Interacting residues
Apigenin	-100	-90.08	-9.92	SER 251, ASP292, ASP 294
4',7-Dimethylapigenin	-102.2	-92.83	-9.35	GLU 192
Apigenin7-O-b-glucuronide	104.13	-90.55	-13.57	HIS 199, IRG 402
Apigenin 4'-O-rhamside	-100.85	-97.11	-3.74	ASN 196

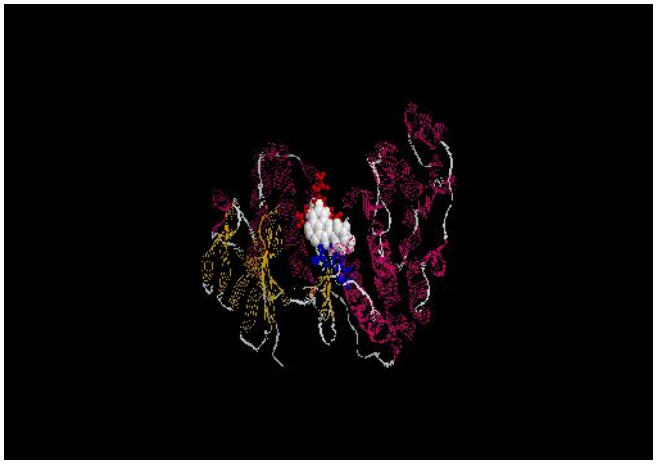

Figure 1: Interaction between apigenin and target protein (MAPK P38)

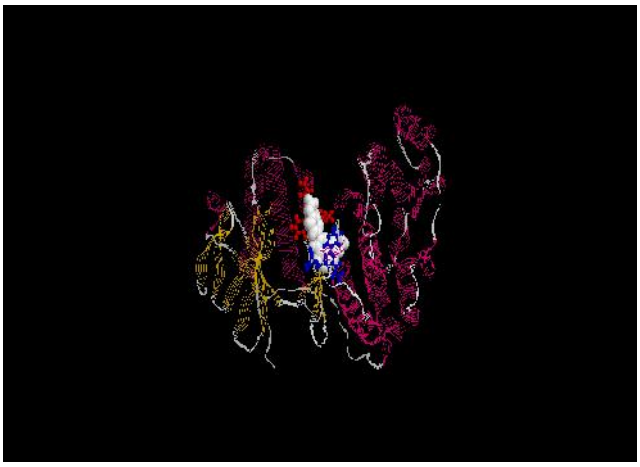

Figure 2: Interaction between 4',7-dimethylapigenin and target protein (MAPK P38)

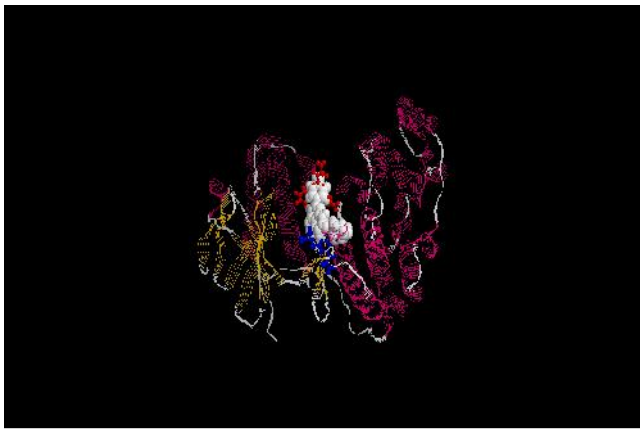

Figure 3: Interaction between apigenin 7-O-b-glucuronide and target protein (MAPK P38)

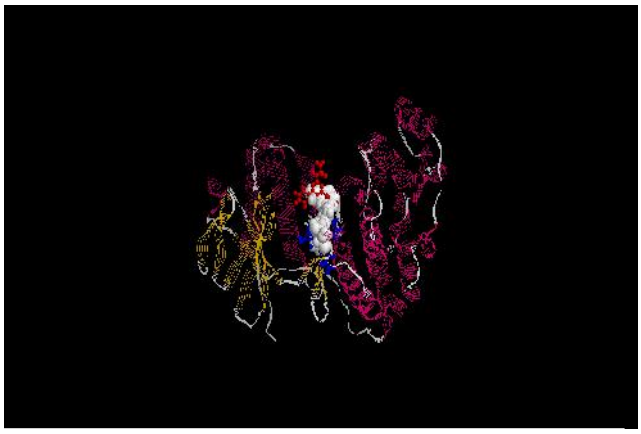

Figure 4: Interaction between apigenin 4'-O-rhamside and target protein (MAPK P38)

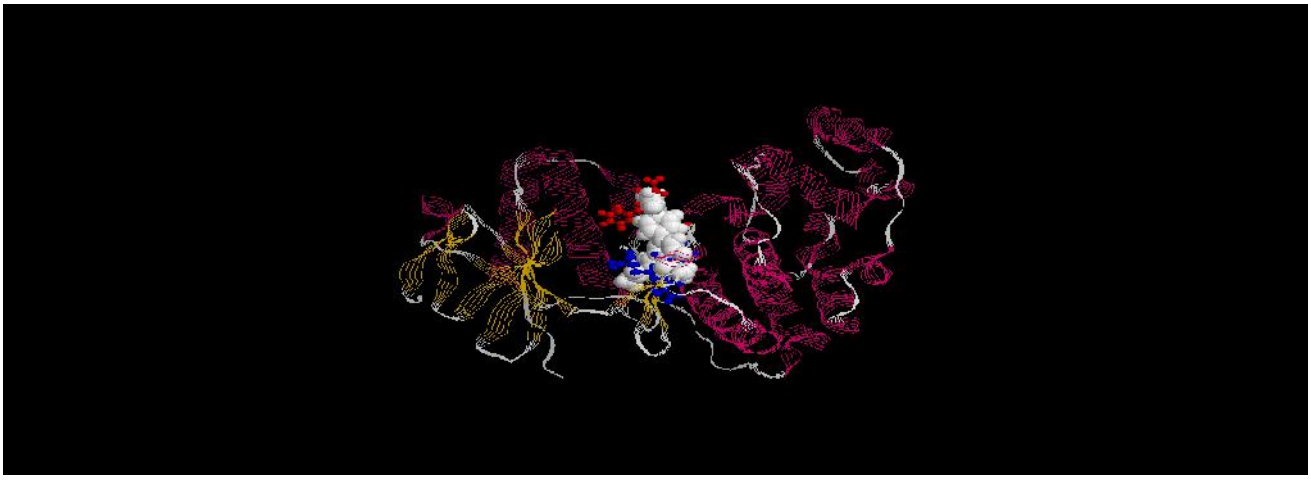

Figure 5: Interaction between apigenin triacetate and target protein (MAPK P38)

such as HIS 199 and IRG 402. When compare with other compounds it has low energy but it also has binding efficiency towards a target. It's hydrogen bond value is -13.57. Result was shown in figure 3.

Interaction between apigenin 4'-O-rhamside and MAPK P38

Apigenin 4'-O-rhamside has an energy level -100.85 KCal/mol, it had interaction with one residue of a target such as ASN 196. When compare with other compounds it has high hydrogen bond value. Its hydrogen bond value is -3.74. Result was shown in figure 4.

Interaction between apigenin triacetate and MAPK P38

Apigenin triacetate has an energy level -95.8 KCal/mol, compare with other compounds it has high interaction energy and it had interaction with two residues of a target such as ASN 196 and SER 251. It's hydrogen bond value is -11.43. Result was shown in figure 5.

DISCUSSION

The idea in molecular docking is to design pharmaceuticals computationally by identifying potential drug candidates targeted against proteins. Mathematically, molecular docking can be formulated as an optimization problem in which the objective is to minimize the intermolecular bound conformational energy of two interacting molecules. The ability of the molecular docking methods to locate selective inhibitors rein forces our over view of structure based drug discovery as valuable strategy, not only for identifying lead compounds, but also for addressing receptor specificity[9].

Molecular docking is a frequently used method in structure-based rational drug design. It is used for evaluating the complex formation of small ligands with large biomolecules, predicting the strength of the bonding forces and finding the best geometrical arrangements[10].

In the present work we proposed and evaluate the interpretation of some forms of apigenins with the target MAPK P38 (P38 Mitogen activated protein kinase) using docking programe GEMDOCK. To study the molecular basis of interactions and binding affinity of natural compounds and their analogues were docked against an active site of MAPK P38 using GEMDOCK. The best compounds were screened out based on the binding energy and their interaction with the receptor molecules. The type of interaction, they exhibit and residues with which they interact convey that they are good inhibitor of MAPK P38.

The result of the current project suggest that all five different forms of apigenins are named as apigenin, 4', 7-dimethylapigenin, apigenin 4'-O-rhamside, apigenin triacetate, and apigenin 7-O-b-glucuronide were proposed here are showing close orientation towards a target protein (MAPK P3), and these compounds can be used as lead for designing further pharmaceuticals that may be used as inhibitor of P38 mitogen activated protein kinase that released by cardiac cells when ischemic attack happens, by inhibiting the target protein there may be a chance for avoiding injury during myocardial ischemia.

In conclusion, the In-Silico studies of the current work prove the inhibition of MAPK P38 protein by natural compound apigenin and it's some other forms. Mitogen activator protein kinase was efficiently inhibited by apigenin. This showed minimal energy on docking against the target hence suggesting the stability of the compound. It is also found to interact well at the active sites of the target. Further studies can be extended to analyses the pharmacokinetics and pharmacodynamics of apigenin in CVD (cardio vascular disease) survivors.

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