INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

MOLECULAR DOCKING STUDIES OF PHYTOCONSTITUENTS ISOLATED FROM *POLYGONUM GLABRUM* AND *BUDDLEJA ASIATICA*

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Article Received on: 03/09/18 Approved for publication: 16/10/18

DOI: 10.7897/2230-8407.0911261

ABSTRACT

In the modern age of substantial development, cardiovascular disease has emerged as the leading cause of death in most parts of India. *Polygonum glabrum* and *Buddleja asiatica* are evergreen shrubs found widely in India. Phytoconstituents such as *3, 5, 7-trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 - one*; *2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione*; *(1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)-3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol*; and *5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one* were isolated from the methanol extracts of *Polygonum glabrum* and *Buddleja asiatica*. The present study was designed to evaluate the phytoconstituents based on their ability to bind with cardiovascular disorder receptors such as Troponin I-interacting kinase (TNNI3K), Calcium/calmodulin dependent protein kinase II (CaMKII) and P 21 activated kinase-1 (Pak 1) by using computational methods (Auto Dock 4.2 software). In the result, a specific ligand *1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol* showed potential binding affinity with TNNI3K and the binding energy was found to be -9.70. Remaining compounds such as *3, 5, 7-trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 - one; 2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione* and *5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one* showed moderate to less binding affinity with target proteins.

Keywords: Molecular docking, TNNI3K, CaMKII, Pak1, *Polygonum glabrum*, *Buddleja asiatica*

INTRODUCTION

Since human arteries are highly vulnerable to ischemic injury or atherosclerotic change, cardiovascular disease has emerged as the leading cause of death in most parts of India, including urban and underdeveloped areas[1].Myocardial infarction occurs when there is a significant reduction or block in the blood supply to the heart, leading to degenaration of a portion of the myocardium. Necrosis of myocytes is the pathological indication of myocardial infarction[2]. TNNI3K, CaMKII and Pak1 are potentially important signaling proteins in the myocardium. TNNI3K is a cardiac specific functional protein kinase which directly interacts with cardiac troponin I[3]. TNNI3K is involved in regulation of membrane potential of mitochondria. It influences the production of reactive oxygen species along with regulating calcium flux in mitochondria (Sharma et al., 2004). Over expression of TNNI3K was observed in myocardial infarction and ischemic injury[4]. TNNI3K mediated cell injury occurred through augmented superoxide production and impaired mitochondrial membrane potential. The detrimental effects of TNNI3K were carried out by activation of downstream effector like p38 mitogen-activated protein kinase [5,6]. P 21 activated kinase-1 (Pak1) belongs to a group of serine/threonine kinases. Pak1 plays a key role in cytoskeleton remodeling, nuclear signaling, cell motility, and cell proliferation[7]. It serves as a ligand to GTP binding proteins cdc42 and Rac. Activation of Pak1 antagonises angiotensin II signaling and β-adrenergic signaling in the heart[8]. An important feature of Pak1 signaling is its association with SA nodal cells, in decreasing the activity of pace maker. Pak1 exhibited its protective effect in SA node by regulation of L-type Ca2+ channels[9]. Increased activity of reactive oxygen species and down regulation of Pak1 expression was observed in isoproterenol induced myocardial infarction. Calcium/calmodulin (Ca^{2+}/CaM) dependent protein kinase II is a multifunctional serine/threonine specific holoenzyme expressed abundantly in heart [10]. CaMKIIα and CaMKIIβ are expressed in neuronal tissues. CaMKIIδ and CaMKIIγ are predominantly found in myocardium. CaMKII phosphorylates a number of proteins responsible for excitation-contraction coupling in cardiomyocytes [11]. It is also involved in calcium mediated cellular functions like regulation of carbohydrate metabolism, activation of ion channels, synthesis of neurotransmitter and maintenance of calcium homoeostasis[12]. Disturbance in Ca^{2+} homeostasis and increased production of reactive oxygen species in myocardium leads to activation of CaMKII. Recent *in vitro* studies showed that β-adrenergic receptor stimulation with isoproterenol can cause cardiomyocyte cell death by activation of CaMKII. Activation of intracellular nitric oxide (NO) by CaMKII lead to Ca2+ leak from the sarcoplasmic reticulum in isoproterenol induced myocardial infarction[13]. Hence, highly selective agonists for Pak1 and antagonists of TNNI3K and CaMKII may serve as a valuable therapeutic tool for alleviating cardiovascular diseases.

In order to make advances in the field of drug discovery many enriched techniques like molecular docking can be used[14]. The frequency of application of molecular docking has improved steadily in recent years. Molecular docking is a process which involves the integration of ligand molecule and a target molecule. The best conformational orientation between the two molecules would be selected based on binding affinity or binding score[15]. This approach leads to easy lead and target identification. Various docking tools such as AutoDock, Glide (Schrodinger), Vina,

Surflex, LigandFit etc. have been used in molecular modeling studies[16]. There are many active sites finding software such as GRID, PASS (Putative Active Sites with Spheres), MMC (mapping macromolecular topography), POCKET, etc. which can detect putative cavity inside the target proteins[17]. The various aspects which lead to accurate docking results are

- Precise prediction of binding site
- Use of compatible docking pose
- Better molecular dynamics to increase docking score
- Selection of correct fit molecule database

Considering all the above facts, the molecular docking studies of isolated phytoconstituents was carried out using three target receptors of myocardial necrosis namely TNNI3K, CaMKII and Pak1.

MATERIALS AND METHODS

Docking softwares

Softwares such as Auto Dock 4.2, Pose viewer, Schrodinger's Maestro visualization program v9.6, Auto Dock Tools version 1.5.6 and Accelrys Software (Version 4.0) were used in the Molecular Docking study.

Ligands/ phytoconstituents

Selected compounds namely *3, 5, 7-Trihydroxy-2-(3, 4, 5-trihydroxyphenyl) -4 H-chromen – 4 – one and 2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione* were isolated from *Polygonum glabrum.* Similarly, *1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol* and *5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one* were isolated from *buddleja asiatica.* The above said compounds were used in molecular docking analysis.

Potential targets and binding site

The crystal structure of potential drug targets such as TNNI3K (PDB ID: 4YFF), CaMKII (PDB ID: 6AYW), and P21-activated kinase 1 (PDB ID: 6B16) were downloaded from the Protein Data Bank (PDB). The binding site or active site in the receptor was detected based on the ligands in their 3D structure. The possible interactions, binding and stability were determined by applying Auto Dock 4.2 software[18].

Protein collection and modification

The 3D structures of potential receptors were retrieved from Protein Data Bank (PDB)[19]. The missing atoms of target proteins were filled with the help of Auto Dock repair command. Before starting semi flexible docking, the crystal structures of receptors were cleaned up by deleting water molecules and adding hydrogen atoms to generate correct ionization and tautomeric states with a stable protein.

Ligand generation

The 2D chemical structure of ligands (phytoconstituents) was drawn using ACD-Chem sktech software. By using Open babel software, 3D structures were converted to structure data format. Accelrys Discovery Studio (Version 4.0, Accelrys Software Inc.) was applied to reduce the energy of selected ligand compounds by using CHARMM force field [20].

Prediction of ligand-receptor interaction

The docked complex formed as a result of the interaction between ligand (phytoconstituents) and target receptors were analyzed with the help of pose viewer software.

Molecular docking studies

Semi-flexible molecular docking was carried out using Autodock 4.2 program. Auto dock Tools version 1.5.6 was used to obtain the structure of ligands and proteins in pdbqt file. Schrodinger's Maestro visualization program v9.6 was employed to analyse the structure of receptors, to calculate hydrogen bonding interactions, to calculate bond lengths and to set the bonds of ligand to be rotatable[21]. A grid box which was large enough to permit the free rotation of ligand was formed. Suitable grid size with dimensions of X: 45.6515 Y: 54.9134 Z: 52.1423 Å, and grid spacing of 0.385 Å, was created. A standard procedure was followed to predict the binding energy and IC_{50} value of the compounds. A total of 10 independent docking runs were performed with each ligand and in each run the pose that showed lowest energy was saved. The ligand binds with the protein through interactions such as hydrogen bonding, π-alkyl, π- anion and π-sigma interactions. After the completion of docking, the conformation pose with best affinity for a molecule was obtained by using Lamarckian Genetic Algorithm (LGA cluster analysis with respective predicted IC_{50}) method. Whenever there was a chance of docking scores appearing close to each other Relative mean square deviation was applied in the selection of best conformation.

RESULTS

Troponin I-interacting kinase (TNNI3K)

The binding energy of phytocompounds docked on troponin I-interacting kinase (TNNI3K) was found to be in the range of -7.35 to -9.70 kcal /mol. (Table 1, Fig 1). For the same target, the standard compound (4CV801), showed a binding energy of -8.32. A minor variation in binding energies were seen between 3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one (-7.35) and 2,3,7,8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione (-7.45). The binding energy of 5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (-7.62) was found to be higher than previously mentioned compounds. However, the compound (1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b – hexadecahydrocyclopenta [a] chrysen-9-ol exhibited remarkably higher binding energy of (-9.70) than the rest of compounds thereby indicating a potential binding affinity with receptor.

Calcium/calmodulin dependent protein kinase II (CaMKII)

As per the molecular docking results showed in Table 2, The compound (1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b – hexadecahydrocyclopenta [a] chrysen-9-ol was noted to have the best estimated binding energy of -6.36 for CaMKII. Comparatively, the binding energy of 2, 3, 7, 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione was found to be -5.42. With the decrease in the interaction between active sites and ligands, less amount of binding energy was observed for 5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (-4.93) and 3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one (-4.13) (Fig 2).

P 21 activated kinase-1 (Pak 1)

In the docking study, all the compounds showed better interaction with Pak1 than the existing standard (fingolimod) (Table 3, Fig 3). The compound (1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol among the other tested compounds exhibited highest binding score of -9.52. The compound 5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one bound to the target protein showed a binding interaction with energy of -6.74. Compounds 2, 3, 7, 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione and 3, 5, 7-Trihydroxy-2-(3, 4, 5-trihydroxyphenyl) -4 H-chromen - 4 - one showed less binding score of -6.46 and -6.41 respectively due to least interaction with the active site.

DISCUSSION

Fundamental understanding of any biosynthetic pathway can lead to development of successful scaffold in drug discovery. Molecular docking is a technical tool which predicts the interaction between a ligand and receptor [22]. In the current study, Auto dock 4.2 was used as the docking program to determine the best conformation between ligand and receptor. Presently, 3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen - 4 - one; 2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione; (1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)-3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol and 5,7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one were used as ligands. Three proteins namely TNNI3K (PDB ID: 4YFF), CaMKII (PDB ID: 6AYW) and Pak 1(PDB ID: 6B16) which were involved in myocardial necrosis were used as target receptors. Hydrogen bondings interactions are generally vital in biological processes as they are involved in enzyme catalysis, protein coding, protein-ligand conformations[23] etc. The study reports suggested that amino acids such as asparagine, threonine, serine and isoleucine were present in the active site of target protein TNNI3K. These amino acid residues were involved in hydrogen bonding with 3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one. In a similar way, amino acids such as leucine, serine and glutamate were involved in hydrogen bonding with 2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione. The compound 5,7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one formed hydrogen bonding with the target protein through amino acids like tyrosine, isoleucine and aspartate. Based on the hydrogen bonding capacity of the receptor atoms ligands can then be redesigned or modified. Ligands with highest affinity may show high pharmacological activity as they are strongly bound to the receptor. The selected flavonoids showed better protein inhibitory activity because of their structural parameters[24]. It was found that hydrophilic amino acid residues of selected target proteins express high binding interactions with flavonoid molecules, as per the theoretical order. Since *polygonum glabrum* consists of many flavonoids, a suitable compound to lower the incidence of myocardial necrosis can be carried by using the molecular docking technique. The exact nature of binding between the receptor and ligand would provide clarity into development of new drugs that target myocardial infarction [25]. Apart from hydrogen bonding interactions, the reactive amino acid in the energy pockets of protein bound to ligands through van der waals interaction. Predicting the mode of binding of a protein with other molecules may pave way to understand the function of proteins ultimately providing new insights to drug discovery. In proteins, van der waals join together to form a energetic contribution[26]. When each of the phytoconstituents was docked with all three protein receptors individually a particular ligand (1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol exhibited outstandingly higher binding affinity with all the selected receptors. The binding energy was found to be -9.70, -9.52 and -6.36 for TNNI3K, Pak1 and CaMKII respectively. The terpenoid skeleton with a methyl groups and methyene group forms the apolar regions of the molecule. They relate with amino acids side chain through van der Waals forces. The probability for van der waals interactions rises due to large surface area of the ligand. The presence of seven methyl groups in the compound 3 increases the surface area of the ligand leading to its strong binding with the receptor[27]. The active site of target proteins of CaMKII was found to contain amino acids residues such as aspartate, valine, leucine, phenyl alanine, alanine, glycine, glutamate, arginine and lysine. By identifying the active pockets of target protein, it is feasible to assess the affinity of the ligand through geometric and physicochemical criteria. Among all the compounds, 3, 5, 7-Trihydroxy-2-(3, 4, 5-trihydroxyphenyl) -4 H-chromen – 4 – one showed least binding affinity with the selected receptors. The remaining two compounds exhibited moderate binding affinity with the target proteins.

CONCLUSION

The present study demonstrated the molecular docking studies of phytoconstituents with selected target receptors. Based on the *in silico* study it is evident that the compound (1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol had more binding affinity with all three receptors. All the remaining compounds possess relatively lesser binding interaction with the target proteins. Hence it can be proposed that the above-mentioned compound should be studied in depth as it has expanded the area of creating promising cardiovascular agents.

Table 1: Docking studies of ligands with TNNI3K

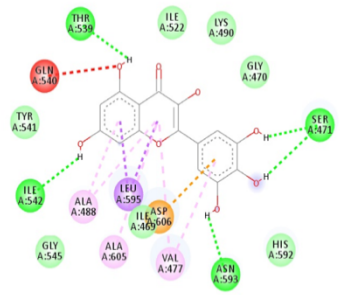
Target protein	Ligands	Binding energy (Kcal/mol)
TNNI3K (4YFF)	4CV801(standard)	-8.32
	3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one	-7.35
	2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione	-7.40
	(1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b –hexadecahydrocyclopenta [a] chrysen-9-ol	-9.70
	5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one	-7.62

Table 2: Docking studies of ligands with CaMKII

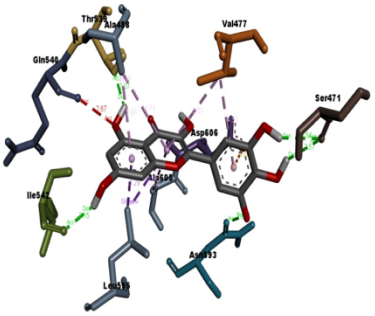
Target protein	Ligands	Binding energy (Kcal/mol)
CaMKII (6AYW)	C2V401(standard)	-5.99
	3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one	-4.13
	2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione	-5.42
	(1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b – hexadecahydrocyclopenta [a] chrysen-9-ol	-6.36
	5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one	-4.93

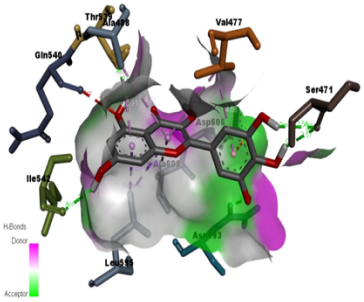
Table 3: Docking studies of ligands with Pak1

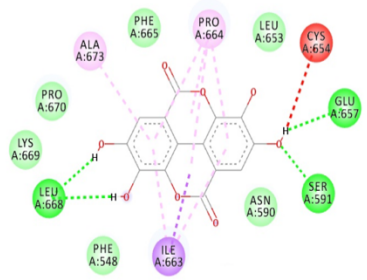
Target protein	Ligands	Binding energy (Kcal/mol)
P21-activated kinase 1 (6B16)	Fingolimod(standard)	-5.48
	3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one	-6.41
	2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione	-6.46
	(1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a, 13b – hexadecahydrocyclopenta [a] chrysen-9-ol	-9.52
	5, 7-dihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one	-6.74



3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) - 4 H-chromen – 4 – one







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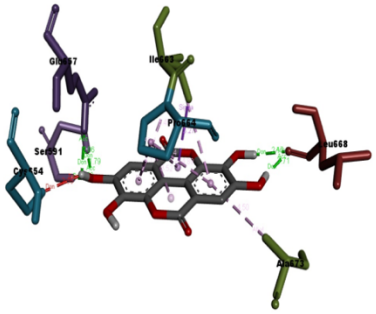

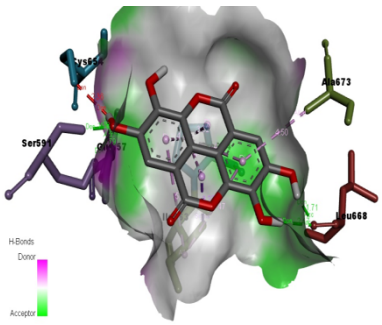

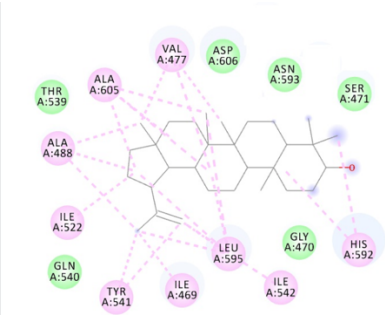

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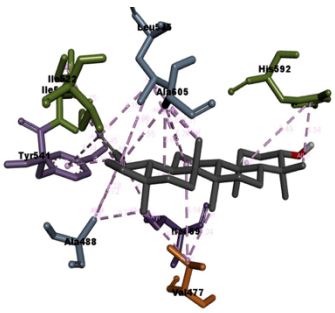
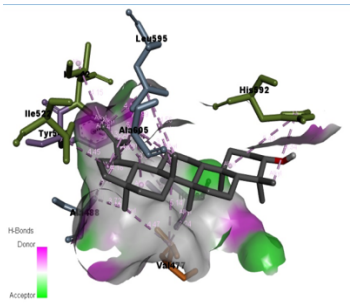
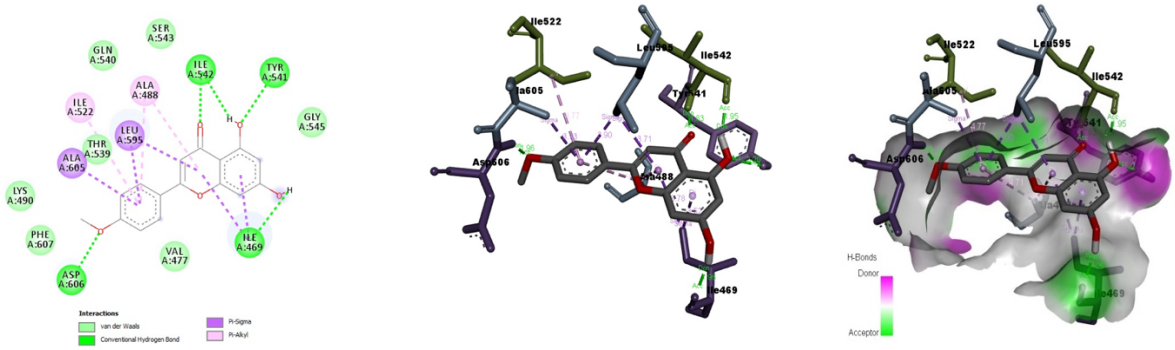
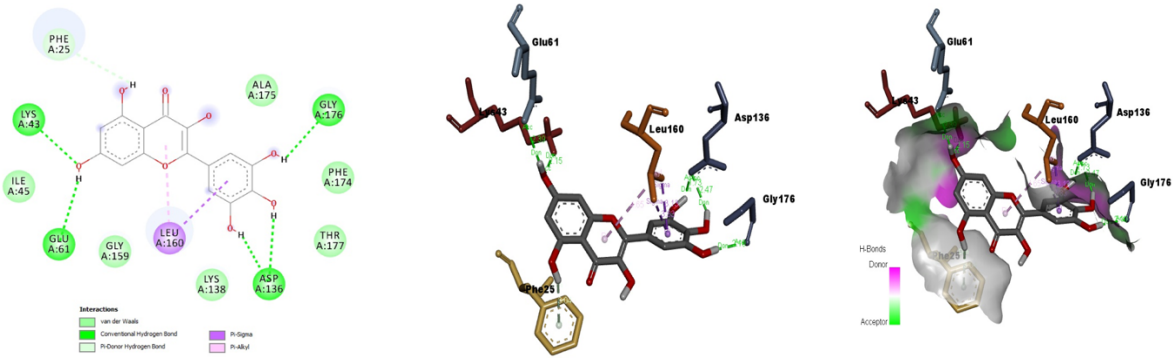




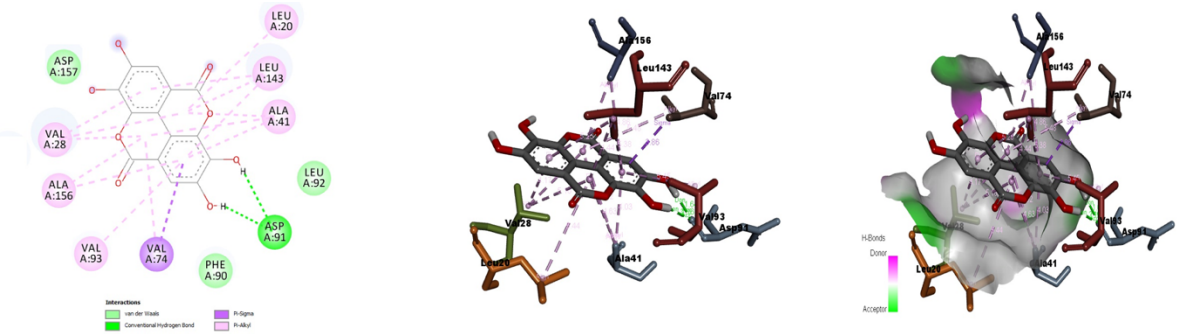


5, 7-dihydroxy-2-(4-methoxyphenyl)- 4H-chromen-4-one

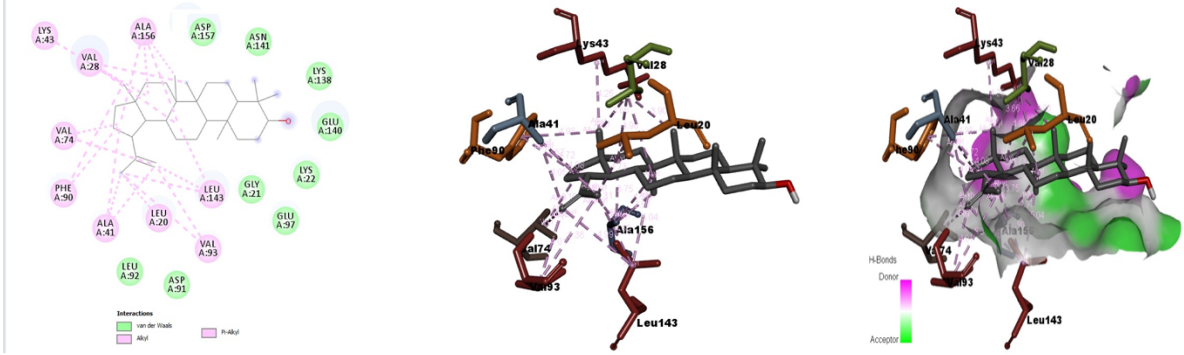
Fig.1: Docking studies of compounds isolated from *Polygonum glabrum* and *buddleja asiatica* bound on the surface of TNNI3K receptor (2D and 3D view)



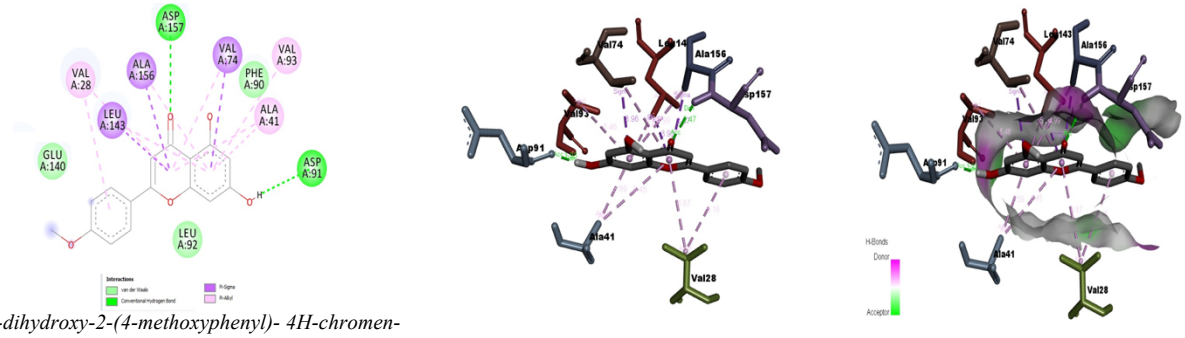
3, 5, 7-Trihydroxy-2-(3, 4, 5- trihydroxyphenyl) -4 H-chromen – 4 – one



2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione

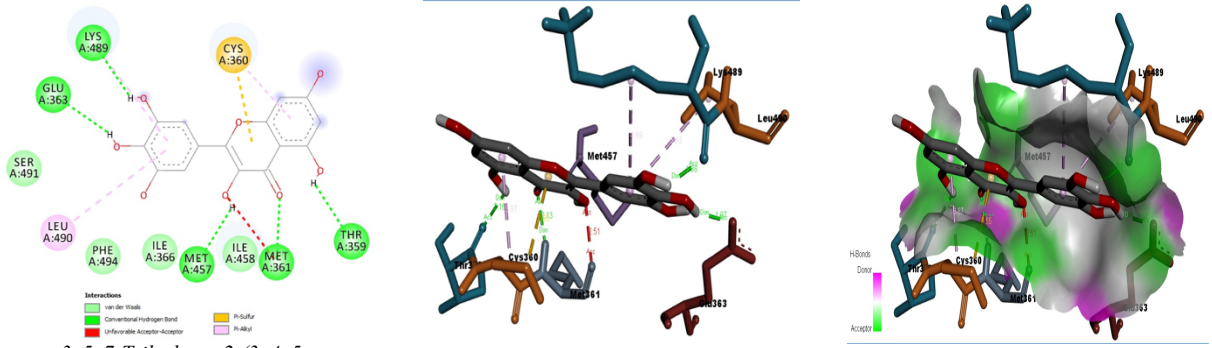


(1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a,13b –hexadecahydrocyclopenta [a] chrysen-9-ol

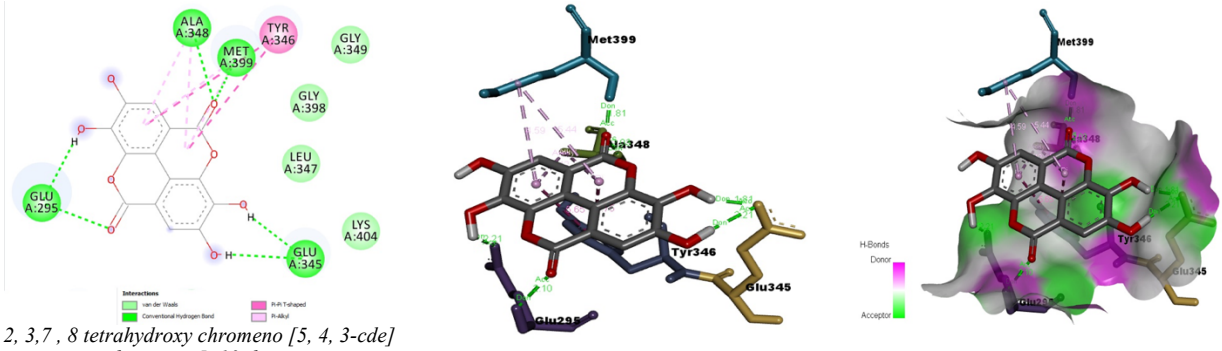


5, 7-dihydroxy-2-(4-methoxyphenyl)- 4H-chromen-4-one

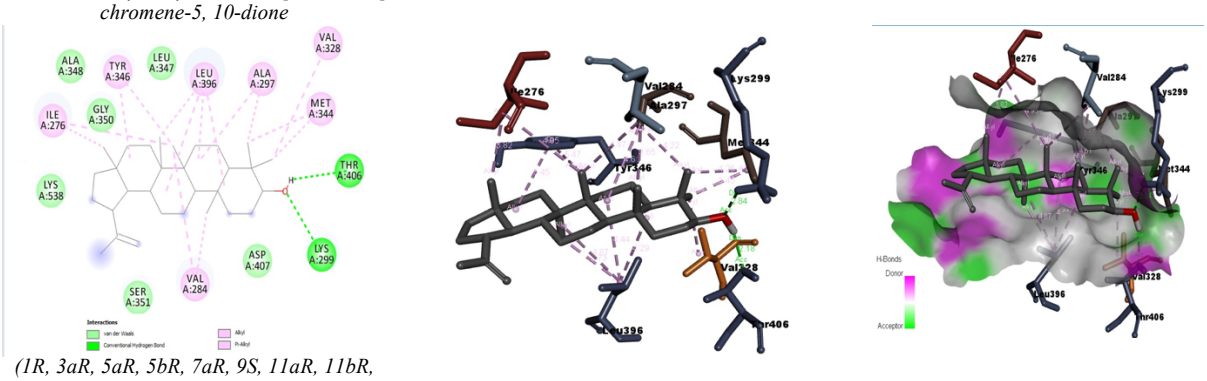
Fig.2: Docking studies of compounds isolated from *Polygonum glabrum* and *buddleja asiatica* bound on the surface of CaMKII receptor (2D and 3D view)



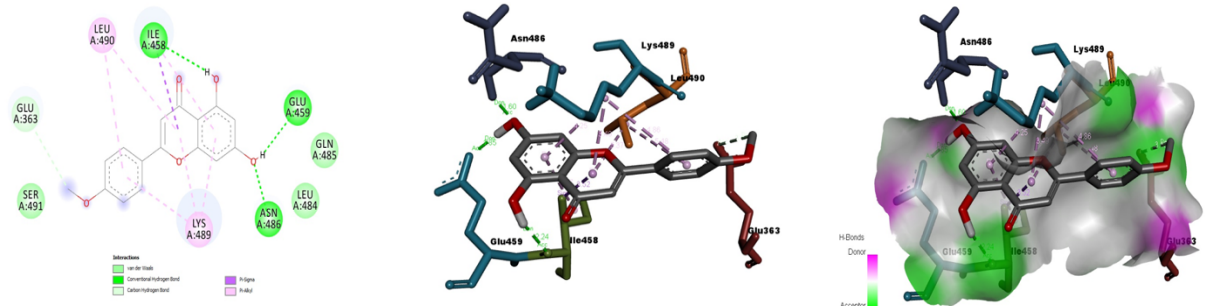
3, 5, 7-Trihydroxy-2-(3, 4, 5-trihydroxyphenyl) -4 H-chromen – 4 – one



2, 3,7 , 8 tetrahydroxy chromeno [5, 4, 3-cde] chromene-5, 10-dione



(1R, 3aR, 5aR, 5bR, 7aR, 9S, 11aR, 11bR, 13aR, 13bR)- 3a, 5a, 5b, 8, 8, 11a-hexamethyl-1-prop-1-en-2-yl-1, 2, 3, 4, 5, 6,7 ,7a, 9, 10, 11, 11b, 12, 13, 13a,13b – hexadecahydrocyclopenta [a] chrysen-9-ol



5, 7-dihydroxy-2-(4-methoxyphenyl)- 4H-chromen-4-one

Fig.3: Docking studies of compounds isolated from *Polygonum glabrum* and *buddleja asiatica* bound on the surface of Pak1 receptor (2D and 3D view

ACKNOWLEDGEMENTS

The authors are thankful to the management of GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India, for providing necessary facilities to carry out the research work.

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Cite this article as:

S. Raja and I. Ramya. Molecular docking studies of phytoconstituents isolated from *Polygonum glabrum* and *Buddleja asiatica*. Int. Res. J. Pharm. 2018;9(11):70-77 http://dx.doi.org/10.7897/2230-8407.0911261

Source of support: Nil, Conflict of interest: None Declared