Available online at www.ijpsdr.com

**International Journal of Pharmaceutical Sciences and Drug Research 2016; 8(3): 144-148**

Research Article

**ISSN: 0975-248X**
**CODEN (USA): IJPSPP**

# Computational Studies of Synthetic and Plant-Derived Compounds against Cardiovascular Disease Targets

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**ABSTRACT**

Knowledge of cardiovascular diseases and improved diagnostic capacity is rapidly expanding with the advancement of medical sciences. However, heart diseases are a challenge to human life. Few important therapeutic targets for cardiovascular diseases were collected from mining of various bibliographic sources. Different proteins and bioactive small molecules are taken into consideration for target search. From ancient times, medicinal plants are shown to have remedial effect on cardiovascular system of human body, yet their modes of action are not completely understood till now. Selected plant derivatives, which have been examined under *in vitro* conditions to be effective against various heart diseases, were subjected to molecular docking with proposed targets using a bioinformatics tool, Hex 8.0. We have explored eight targets for five types of cardiovascular diseases and ten different ligands from herbal plants with a brief description about the cardiovascular diseases, their symptoms, target, ligand, source of the ligand and their mechanism of action. All the reported synthetic and phytocompounds were found to have good binding energies with all potential disease targets. Among all, Forskolin is found to be the best inhibitor of Angiotensin II type I receptor with the E-score of -369.96 for Atherosclerosis.

**Keywords:** Molecular docking; cardiovascular; Hex; phytocompounds.

## INTRODUCTION

Cardiovascular diseases (CVD) are the group of disorders of heart and circulation, responsible for premature death. CVDs include: ischemic heart disease (IHD), stroke, hypertensive heart disease, rheumatic heart disease (RHD), aortic aneurysms, cardiomyopathy, atrial fibrillation, congenital heart disease, endocarditis, and peripheral artery disease (PAD). Risk factors of CVDs are mainly unhealthy diet, lack of physical activity, high blood pressure, high blood cholesterol, diabetes, smoking, obesity and sometimes-family history. According to WHO (Fact sheet N°317, 2015), 17.5 million people died from CVDs in 2012, which is the 31% of all worldwide deaths. Among these, coronary heart disease was responsible for 7.4 million deaths and 6.7 million were died due to stroke. However, CVDs are no more age related disorders; still most of the cardiovascular diseases affect older persons. We have studied five important cardiovascular diseases, which are important and seek global attention. These are cardiomyopathy (heart muscle disease) is the decrease in the ability of the myocardium (the heart muscle) to contract, mostly resulting in heart failure. Myocardial infarction (Pain), commonly known as a heart attack, is the damage of heart muscle, occurring when blood does not flow to the heart on any part of it. Coronary artery disease (CAD) is also known as ischemic heart disease (IHD).

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**Received:** 28 March, 2016; **Accepted:** 10 May, 2016

Atherosclerotic or coronary heart disease includes symptoms like stable and unstable angina, myocardial infarction as well as sudden artery death. Myocardial Ischemia (MI), a heart condition, occurs through decreased blood flow to the myocardium due to a partial or complete blockage of coronary arteries. Blood clotting disorder is the condition of shock and possible death when the loss of blood from the damaged or cut blood vessels was not stopped.

CVDs are the consequence of multiple pathogenic factors, reflecting the changed interaction between interconnected genes and their products. A number of chemicals, synthetic drugs, NSAIDs have been used to cure CVDs but demand for compounds with lesser side effects is increasing. In addition to the tremendous growth of biochemical data and the progress of network pharmacology, the analysis of mechanisms of action of medicinal herbs at *in silico* level has become possible. Walker (1996) has reviewed plant foods and extracts for prophylactic and curative effects in reducing cardiovascular disease. [1] Table 1 shows all studied targets their ligands, source of ligand and their corresponding associated diseases.

Literature survey reveals that the majority of current CVD drugs develop adverse effects. On the contrary, natural and few industrially produced compounds contain the remedial properties without any harmful effects on human being even after long-term use. These compounds can play a vital role in the production of novel treatment amenity for cardiovascular diseases. Therefore, objective of the present study is to identify the inhibitors having the potential to inhibit various targets of cardiovascular diseases and explore their interaction capability with selected ligands. In the present study, we worked on eight potential molecular targets for five types of cardiovascular diseases and docked them with ligands of medicinal plants and safe synthetic compounds to test their binding affinity for probable phytomedicine as well as synthetic but harmless drug for humans. The selected ligands are Forskolin (Fig. 1), Naproxen (Fig. 2), Pinocembrin (Fig. 3), Resveratrol (Fig. 4), Morin hydrate (Fig. 5), Tamarixetin (Fig. 6), Epicatechin (Fig. 7), Cocoa flavanols (Fig. 8), Cannabidoids (Anandamide) (Fig. 9) and Aspirin (Acetylsalicyclic acid) (Fig. 10). Except naproxen and aspirin all are plant-derived compounds. Various bioinformatics tools like Swiss prediction, Hex, OpenBabel Graphical User Interface (GUI), various databases (uniprot, PDB, RCBS, NCBI), pc3 viewer and argus lab have been used to explore the findings.

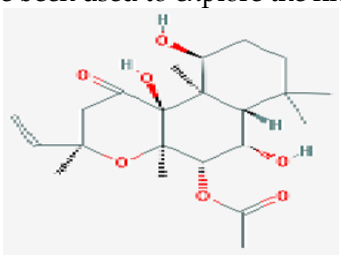

**Fig. 1: Forskolin**

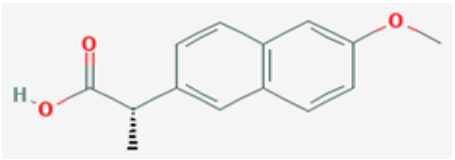

**Fig. 2: Naproxen**

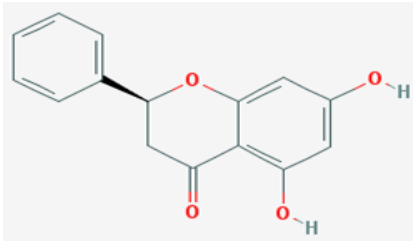

**Fig. 3: Pinocembrin**

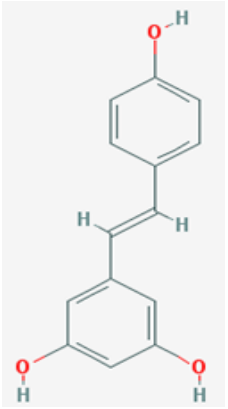

**Fig. 4: Resveratrol**

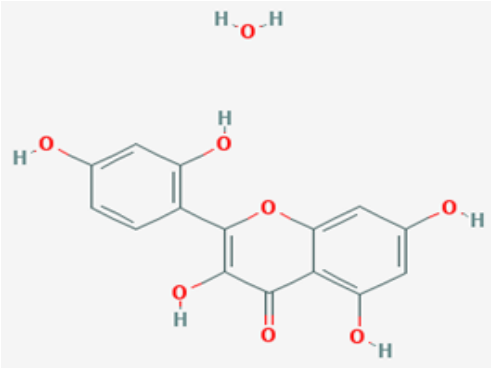

**Fig. 5: Morin Hydrate**

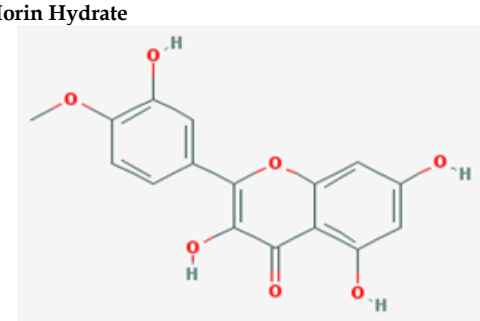

**Fig. 6: Tamarixetin**

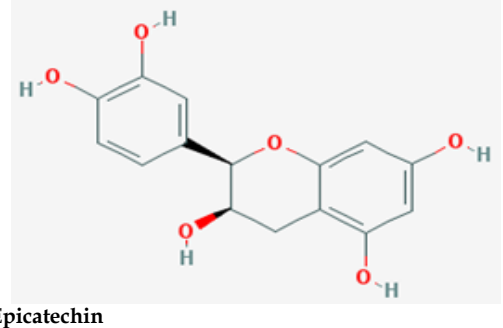

**Fig. 7: Epicatechin**

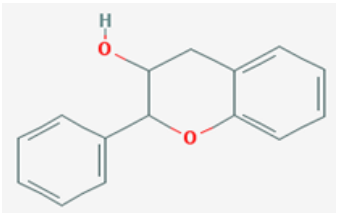

**Fig. 8: Cocoa Flavanol**

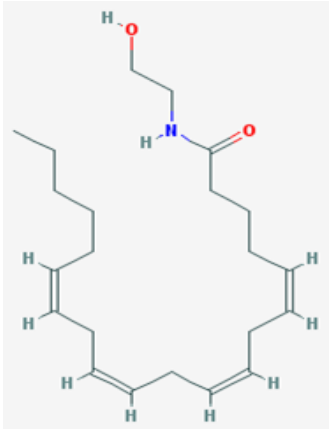

**Fig. 9: Anandamide**

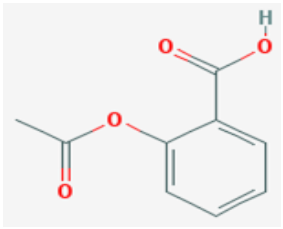

**Fig. 10: Aspirin**

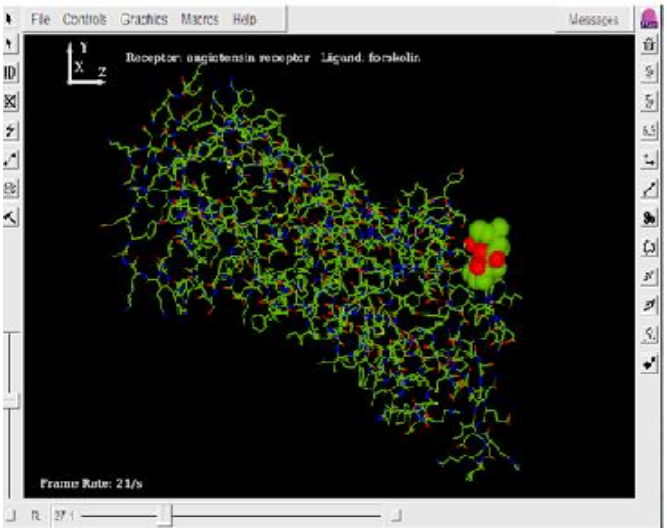


**Fig. 11: Docked complex of ATR and Forskolin (red and green balls)**

## MATERIALS AND METHODS

### Inverse (or reverse) docking (for target prediction)

Molecular docking is a computational process, which helps to determine the energy associated with a ligand-target complex and how the energy level changes according to configuration in the form of E values. Once the genes responsible for causing diseases are found, it would be possible to design lead molecules, which could modulate those genes or their protein products. The growth in the number of 3D structure databases of proteins eg. PDB and the increase in computing power have made virtual screening of lead molecules an easier and faster process. However, in reverse docking, protein targets are searched, which can bind to a specific known ligand. The procedure is as follows -a compound with known biological activity is docked to the binding sites of all 3D structures of proteins in a given database. Protein 'hits' identified from this docking can further be used as potential candidates for validation. This approach is referred to as reverse docking. The software that was used to do reverse docking was SwissTargetPrediction.

### Ligand preparation

The 3D structures of the 10 plant derived compounds were obtained from PubChem in PDB format. The ligands were available in XML, SDF, JSON and ASN.1 formats. Most structures were obtained in SDF format. These conformations were used as starting conformations to perform docking. [2]

### Target preparation

Most appropriate targets were obtained through Swiss target search. Secondary research via literature survey has been done for the validation of the selected targets. Target structures were obtained from Protein Data Bank in PDB format. Targets were downloaded in such a way that heteroatoms like water, ions etc. were not present and they did not complex with other bioactive molecules. Those structures, which were found complexes with other bioactive molecules, were individually modeled using SWISS MODEL. It uses the FASTA format of protein sequences. [2]

### Ligand visualization

The ligand and target in the PDB format were visualized in Argus Labs [3] and in PC3 viewer. ArgusLab and PC3 viewer are both freely licensed. The structure files obtained from ChemSketch, Pubchem were not in PDB format. They were converted to PDB format using OpenBabel. Molecular Docking technique was done using Hex 8.0.0 with 10 plant-derived compounds. Hex is an interactive molecular graphics program used for calculating and displaying feasible docking pairs of protein-DNA or, protein-ligand molecules, assuming the ligand is rigid.

## RESULTS AND DISCUSSION

Each compound was docked to the same or a different target. In order to compare docking interactions between selected natural compounds and the known inhibitor/activators (as required) of each target, docking was also performed with specific compounds that are reported to have activity against the studied targets, via previous studies. Table 2 shows the E-score of all interactions.

Docking results for binding between Adenylate cyclase and Forskolin showed adequate binding. Adenylyl cyclase (AC) is an effector molecule that catalyzes the conversion of ATP to cAMP in β-adrenergic receptor (βAR) signaling. Forskolin has the ability to activate cAMP-generation systems reversibly in intact cells. It acts as an activator for adenylate cyclase.

**Table 1: Cardiovascular diseases their therapeutic targets and corresponding ligands**

| S. No. | Disease | Target | Ligands | Source of Ligand |
|---|---|---|---|---|
| 1 | Atherosclerosis/Coronary Artery Diseases | Angiotensin II type 1 Receptor [14] | Forskolin | Plant- *Coleus forskhohlii* |
| | | | Resveratrol | Plant- grapes, nuts and berries |
| | | | Morin hydrate | Plant- *Morus alba L.* |
| | | | Tamarixetin | Plant- *Tamarix gallica* |
| | | NF-κB | Epicatechin | Plant-*Theobroma cacao* |
| | | | Quercetin reductase [15] | Plant-*Theobroma cacao* |
| | | | Cocoa Polyphenols [16] | Plant-*Theobroma cacao* |
| | | | Cocoa Flavanols | Plant-*Theobroma cacao* |
| | | Angiotensin Converting enzyme (ACE) | Epicatechin | Plant-*Theobroma cacao* |
| | | | Cocoa flavanols | Plant-*Theobroma cacao* |
| | | SOD | Epicatechin | Plant-*Theobroma cacao* |
| | | | Cocoa flavanols | Plant-*Theobroma cacao* |
| 2 | Blood Clotting | Thromboxane $A_2$ [17] | Aspirin | Synthetic- Industrially produced |
| 3 | Cardiomyopathy [18] | Adenylate cyclase | Forskolin | Plant- *Coleus forskhohlii* |
| 4 | Myocardial Infarction, Pain | COX-2 | Naproxen [19] | Synthetic-Industrially produced |
| | | | Pinocembrin | Plant- *Curcuma ecalcarata* |
| | | | Resveratrol | Plant- grapes, nuts and berries |
| 5 | Myocardial Ischaemia | Cannabinoids Receptor 1,2 [20] | Cannabinoids | Plant-*Cannabis sativa* |

**Table 2: E-score of all docking interactions performed for cardiovascular disorders**

| S. No. | Targets | Ligands | Total E-score |
|---|---|---|---|
| 1 | Adenylate cyclase | Forskolin | -313.3 |
| 2 | Angiotensin II type 1 Receptor | Forskolin | -369.96 [Figure 11] |
| 3 | Angiotensin Converting enzyme | Anthocynidine reductase | -769.9 |
| 4 | Cannabinoids Receptor 1,2 | Anandamide | -344.4 |
| 5 | COX-2 | Naproxen | -289 |
| | | Resveratrol | -351.0 |
| | | Pinocembrin | -286.97 |
| | | Resveratrol | -280.5 |
| | | Morin hydrate | -325.3 |
| 6 | NF-KB | Anthocynidine reductase | -245.4 |
| | | Quercetine reductase | -325.6 |
| 7 | SOD | Anthocynidine reductase | -879.1 |
| 8 | Thromboxane $A_2$ | Aspirin | -132.85 |

Forskolin elicited marked accumulations of cyclic AMP in rat cerebral cortical slices. [4] Naproxen binds to cyclooxygenase-2 (COX-2) with good interaction energy. All three ligands have been reported as inhibitors of COX-2. The inhibitors suppressed the formation of prostaglandin $I_2$ as COX-2 was the source of prostaglandins $E_2$ and $I_2$, which mediate inflammation. [5] The selective inhibition of this target has been shown to relieve patients of myocardial infections. AT1 (Angiotensin II type 1 receptor) is a well-known vasconstrictor, which causes blood vessels to constrict thereby causing hypertension. Angiotensin II receptor blockers (ARBs) prevent ligand angiotensin II to bind these receptors on blood vessels, providing relief in atherosclerosis. [6] Here, many plant derivatives were found to play this role. Forskolin, Resveratrol, and Morin hydrate have good binding with AT1. Forskolin is found to be the best inhibitor among all docked ARBs. Fig. 11 shows docked complex of angiotensin II type I receptor and Forskolin (red and green balls). Binding of Anthocynidine reductase to SOD leads to its activation. SOD is produced in more amounts. E-score of this interaction is good interaction. *In vivo* interaction between ROS and RNS, results in the formation of peroxynitrite (a powerful oxidant). [7] The reaction between SOD and reactive oxygen species prevents interaction between ROS and NO. Thus, maintaining concentration of NO that is a vasorelaxant. [8] This is beneficial against atherosclerosis. Another target in Atherosclerosis is angiotensin converting enzyme (ACE). Angiotensin-converting enzyme (ACE) inhibitors interfere with the formation of Angiotensin II that can constrict blood vessels. ACE inhibitors lower B.P. and reduce the workload on the heart, which lowers the chances of heart attack. Anthocynidine reductase showed good inhibition when complexes with ACE. Anandamide, an endocannabinoids was docked with CB receptor 1 and resulting complex showed inhibition of the receptor. Cannabinoids provide protective role in atherosclerosis progression and in cerebral and myocardial ischemia. [9-11] Anandamide limits infarct size induced by ischemia-reperfusion injury and the pharmacological profile of this response fails to match with any of the previously known mechanisms of cannabinoid action. [12] Thromboxane-$A_2$ is the therapeutic target of blood clotting disorder [13] and its ligand Aspirin is helpful in giving relief from skeletal pain, viz. arthritis, fever (antipyretic), prevents platelet coagulation (thus used for preventing heart attacks) and inhibits prostaglandin synthesis. As such, its role is being studied in diseases where blood clotting blocks vessels. Binding with target thromboxane A2 is noticed as least effective.

Among all docked complexes, ligand anthocynidine reductase showed maximum E-score with target SOD (super oxide dismutase) by activating it (or increasing its production) while ligand Forskolin shows maximum E-score with target Angiotensin II type I receptor by activation of target. As such, these interactions have high binding affinity and can be further studied for their role as potential molecular targets in targeted treatment of cardiovascular diseases. However, all the

studied docked complexes can be referred for development of potential drugs for cardiovascular diseases. Experimented computational technique is faster than the traditional drug designing method, cheaper and less laborious. Results of this investigation can further be utilized for the development of safe and potent herbal and synthetic drug after *in vivo* studies and clinical trials to the benefit of humankind.

**ACKNOWLEDGEMENT**

We would like to thank Vice Chancellor of Delhi Technological University and Head of Department of Department of Biotechnology, for providing the facility and support to conduct the research work.

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**Source of Support: Nil, Conflict of Interest: None declared.**