ORIGINAL RESEARCH

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In-Silico Study of Chicoric acid as an Adjunct Therapy Targeting Caspase-3 for Effective Management of Heart Failure

Jyotirmaya Sahoo[1]*, Nabeel Ahmad[2], Anuradha Singh[3]

[1]School of Health & Allied Science, ARKA JAIN University, Jharkhand, India

[2]School of Allied Science, Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand, India

[3]Department of Bio-Sciences, Galgotias University, Greater Noida, Uttar Pradesh, India

*Corresponding author:
dr.jyotirmaya@arkajainuniversity.ac.in

Abstract

Heart failure is a significant public health problem and it is one of the most prevalent reasons for being admitted to the hospital. It mostly affects the elderly, and with rising life expectancy and better management of chronic medical diseases, the patient population with heart failure is predicted to rise. As there are many side effects of existing drug interventions that are being used to manage the heart failure issue, the surge to explore alternative traditional medicine has regained all interest. Therefore, this study aims to identify a potential inhibitor of a novel target for heart failure "caspase-3" which plays an important role in the failing of the heart using a computational approach of molecular docking. The study explores the targeting ability of chicoric acid which is one of the phytocompound presented in various botanical sources having cardioprotective nature. The results of the study revealed a negative binding affinity of -15.46Kcal/mol which is promising for the development of alternative treatment or an adjunct for effective heart failure management.

Keywords

Cardiovascular disease (CVD), Chicoric acid, Caspase-3, Drug target, Heart Failure

Imprint

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1. INTRODUCTION

The aging of populations, distribution of diseases, the frequency of risk factors for non-communicable diseases, causes of death, mortality, life expectancy, and socio-demographic variables are all changing worldwide. The leading cause of morbidity and mortality globally is cardiovascular disease (CVD) [1], [2]. The term «cardiovascular disease» (CVD) refers to a variety of disease conditions that affect the heart. CVD is frequently misunderstood to be a single disease. The heart, blood vessels, and cardiac muscle are all affected by several serious diseases rather than just one. Rheumatic heart disease, stroke, coronary heart disease, angina, and other conditions are examples of these diseases. These diseases cause hundreds of thousands of deaths each year. An estimated percentage of deaths due to different cardiovascular diseases in 2016, is illustrated in Figures 1 [3]–[5].

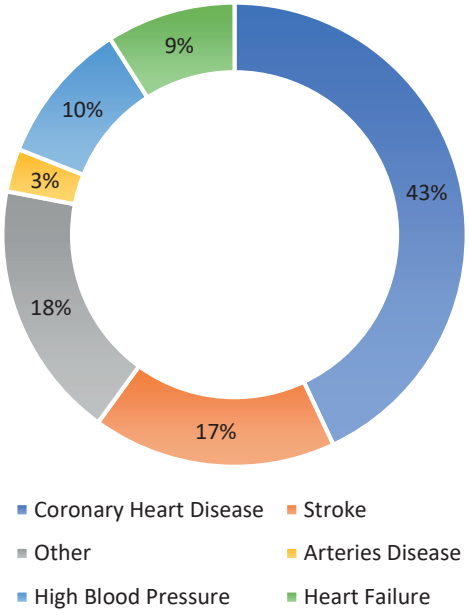

Figure 1: Illustrating Estimated Deaths due to Different Cardiovascular Diseases; 2016.

The most common clinical manifestation of CVDs in their advanced stages is heart failure, which can develop when the capacity of the ventricle to pump blood is compromised. Myocardial infarction, various ischemic heart conditions, valvular heart disease, hypertension, and cardiomyopathy are some of the fundamental causes of heart failure [6], [7]. Despite

accounting for only 17% of deaths, it accounts for a major burden on healthcare resources for its management and prevention. In addition to the higher survival rate following myocardial infarction, patients with cardiovascular risk factors including diabetes mellitus, obesity, hyperlipidemia, and arterial hypertension, are becoming more common, which is contributing to the rising prevalence of heart failure [7].

Heart failure is seen as a progressive condition that begins with an index event. Myocardial infarction, viral infection, severe arrhythmia, prolonged hypertension, high level of stress, or hereditary disease are all examples of index events. Finally, the index event causes cardiomyocyte damage, leading to loss of function or failure in cardiac pumping. Heart failure is an unquestionably serious public health and clinical issue. Despite recent advancements in treating heart failure and related underlying diseases, it remains a very frequent and fatal disorder due to rising life expectancy throughout cultures [8].

Cardiomyocyte loss is one of the important hallmarks in the progression of milestones and the development of heart failure. The heart cannot maintain effective contraction with fewer myocytes. In failing hearts in both human patients and animal models, apoptosis is one of the main processes driving cardiomyocyte loss [9]. Although the fundamental reason and pathophysiology significance of apoptosis are unknown, anti-apoptosis has therefore been put out as a thought-provoking new paradigm for both preventative and treatment interventions for heart failure [10]. By promoting the breakdown of myofibrillar proteins, caspases accelerate the gradual loss of contractile function in heart failure. Selective suppression of caspase-3 proteolytic activities may provide an appealing strategy for preventing or reversing heart failure. Many drug interventions such as diuretics, ACE inhibitors, and β-adrenergic receptor blockers are all employed to treat and manage the consequence of heart failure. However, some side effects become barriers to their use and ineffective management [11], [12]. Therefore, the compounds are now being explored from natural sources, especially of plant origin which can further help in the development of drugs effective in preventing heart failure [13].

This present study aims at identifying possible photoinhibition against caspase-3 which can further help in managing the burden of heart failure in a population with increasing life expectancy.

2. LITERATURE REVIEW

In a study carried out by Kumar *et al.*, *Terminalia arjuna* was evaluated for its phytochemicals as cardioprotective nature for cardiovascular diseases. They retrieved the 3D structure of different target proteins responsible for the development of cardiovascular diseases including chronic heart failure and performed docking of a total of 19 phytocompounds. The results of their study revealed that the compound the causuarinin demonstrated the promising negative energy of -24.0kcal/mol which is promising to develop an alternative medicine against heart failure [14].

Nurhafsyah *et al.* investigated natural compounds for effective neprilysin inhibitors as an adjunct for the treatment of CHF. In their study, they used PubChem and RCSB PDB for the retrieval of protein and standard ligand structure. The structure of the Indonesian test compound was taken from an herbal database. The results of their study revealed that the herbal compound NSC93241 (-7.07 ± 0.05 Kcal/mol) had comparable and even more binding affinity against NEP when compared to the standard drug sacubitril ((-6.73 ± 0.06 Kcal/mol) [15]structure of NEP was obtained from Protein Data Bank (5JMY.

Huang *et al.* carried out a herbal formulation known as QiShenYiQi which has shown to effective against "Heart failure with preserved ejection fraction (HFpEF)". The study evaluating the effects of developed herbal products is carried out on mice models, the results of which are studied in terms of hemodynamics, echocardiography, leukocyte infiltration, and oxidation stress. The results of their study revealed that the developed herbal formulation was able to inhibit "microvascular endothelial inflammation" and activate the "NO-cGMP-PKG pathway" [16].

3. METHODOLOGY

3.1. Design

To identify the possible and effective ligand structure to manage heart failure with alternative medicine a data mining and thorough review of existing literature was carried out. The present study uses a computational approach and docking process to explore the targeting ability of selected ligands and target proteins. After performing data mining and an intensive review of the literature revealed caspase-3 as a potential target protein for heart failure and Chicoric acid as an inhibitor. To carry out the study the protein and compound

were retrieved from respective database which was then prepared for docking and the docking was performed using Autodock4 followed by the visualization of the complex by a separate tool called BIOVIA Drug Discovery Studio (Figure 2).

3.2. Instrumentation

To retrieve the structures of protein and ligand, RCSB: PDB and PubChem database are used. The "Research Collaboratory for Structural Bioinformatics" is the elaborated form of RCSB whereas the Protein Data bank is an elaborated form of PDB (http://rcsb.org). It is the center for the worldwide PDB repository and provides PDB data available for free for all researchers which can include various medical professionals, and beyond. It serves as a repository for the 3D structural information of major biological molecules like nucleic acids as well as proteins. The data, often collected by NMR spectroscopy, or, increasingly, cryo-electron microscopy, X-ray crystallography is contributed by biochemists and biologists from throughout the world.

PubChem is a compendium of chemical compounds and associated biological assay activities. The system is overseen by the "NCBI" which stands for "National Center for Biotechnology Information", a division of the National Library of Medicine, which itself is part of the National Institutes of Health in the United States (NIH). PubChem is available for free via a web interface. Millions of chemical structures and descriptive information are freely available for download

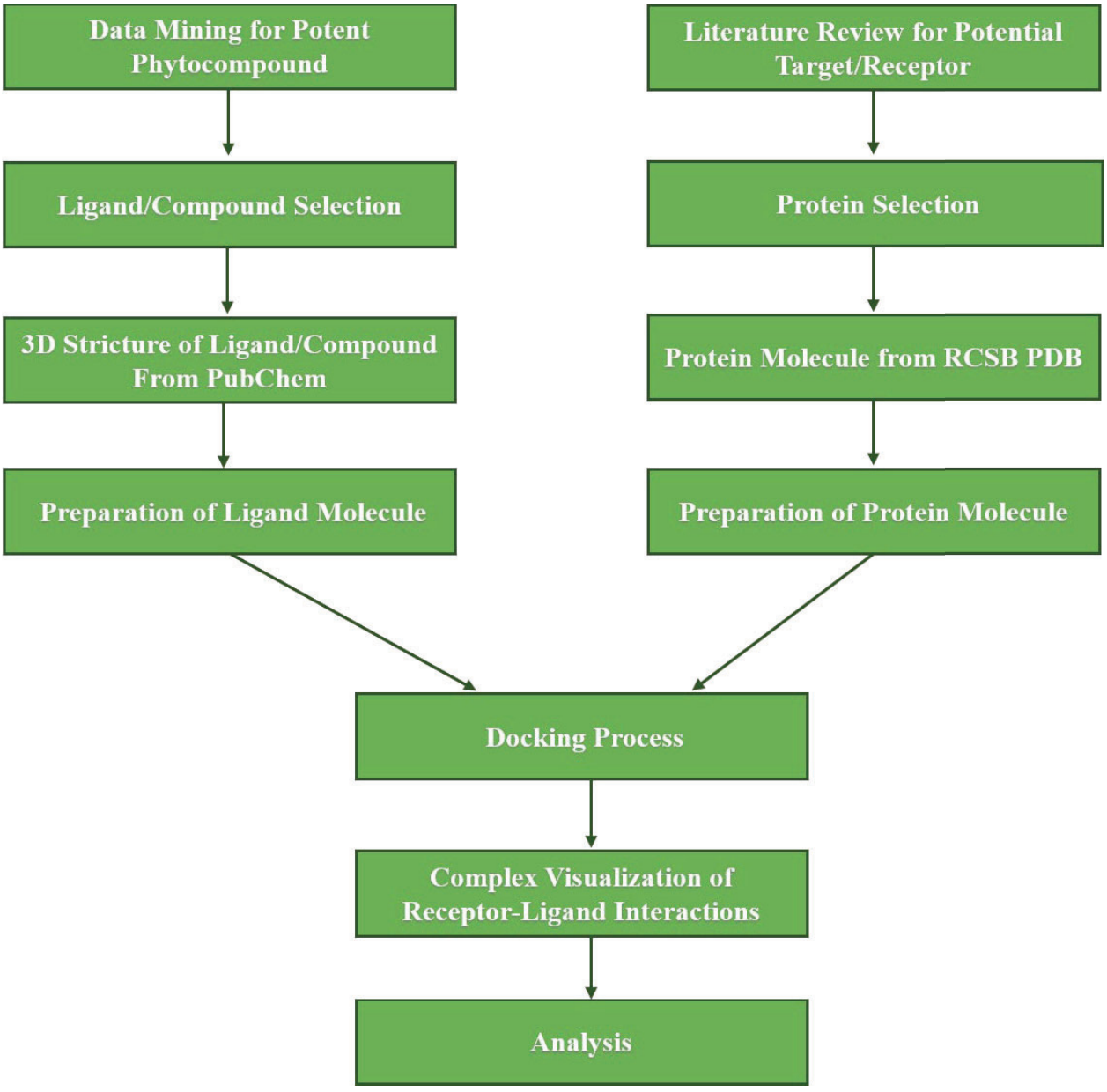

Figure 2: Illustrating the Methodology Used to Carry Out the Docking Process.

through FTP. PubChem contains a variety of substance descriptions as well as small compounds with less than 100 atoms and 1,000 bonds. Over 80 database providers contribute to the ever-expanding PubChem database.

For the molecular docking process, Autodock4 was used which is one of the most cited software in the research community. The software analyzes receptor-ligand interactions and predicts how a compound or a ligand will bind to a protein or a receptor in a living biological system by providing docked log file which is then analyzed by the use of a visualization application called BIOVIA drug discovery studio.

3.3. Collection and Preparation of Sample

3.3.1. Ligand Collection and Preparation

The ligand molecule is retrieved for PubChem in. XML format which was then converted into .pdb format using a simple tool called open babel GUI which is freely available and easily accessible. The compound was exported to the Autodock tool for further preparation. After carrying out the ligand preparation, the ligand was then saved in the format of .pdbqt which is a must to carry out a further process of docking. The structure of the ligand molecule is provided in Figure 3 below.

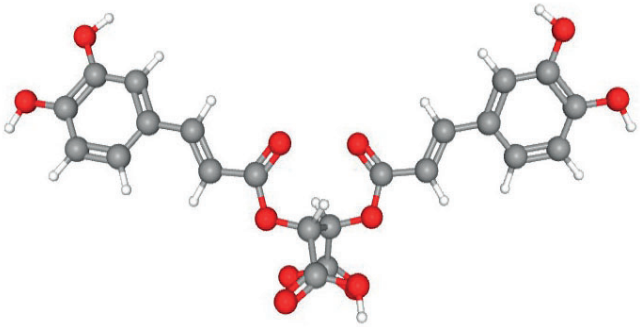

Figure 3: Illustrating the ball and Stick Structure of Chicoric acid; Grey Balls Represents Carbon, Red Represents Oxygen and White Represents Hydrogen Molecules.

3.3.2. Protein collection and Preparation

The structure of the protein caspase-3 with PDB ID: 3H0E was obtained in .pdb format from RCSB PDB which was then pruned to eliminate the attached ligand molecule as well as the water molecule. The molecule was then exported to Autodock where further preparation was carried out with the addition of polar hydrogens to make the docking process efficient, The protein molecule was then saved in .pdbqt format for further docking process. The 3-D structure of the protein is illustrated in Figure 4 below.

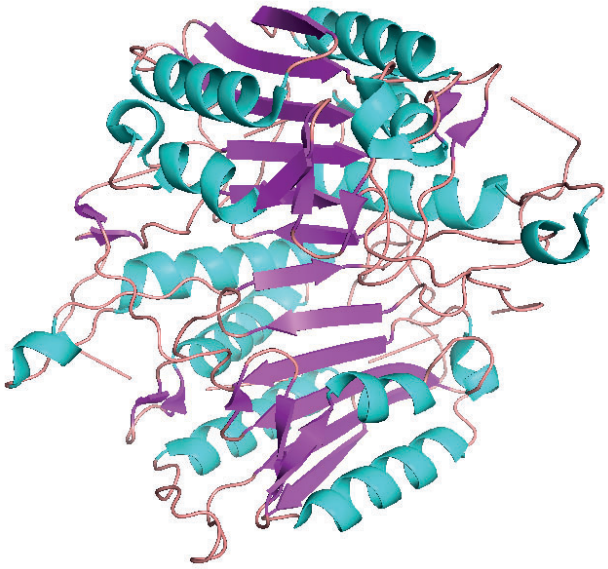

Figure 4: Illustrating the three-dimensional Structure of Protein Where the Magenta Color Represents the Beta-pleated sheet and Cyan Colored Helical Structures Represent the Alpha-helices.

3.4. Data Collection

Docking of protein and selected ligand is performed to generate several confirmations and positions for effective binding of protein and ligand to form the complex. To perform the docking process, first, the auto grid was run by using the .gpf file which was then followed by running autodock4 using the .dpf file. The docking was performed by making a protein or the macromolecule as rigid and ligand as flexible. The autodock tool was used to obtain the binding energy of different docked confirmations in the DLG file. The confirmation with the most negative binding energy was used to show the interaction as illustrated in Figure 5 which was followed by a writing complex.

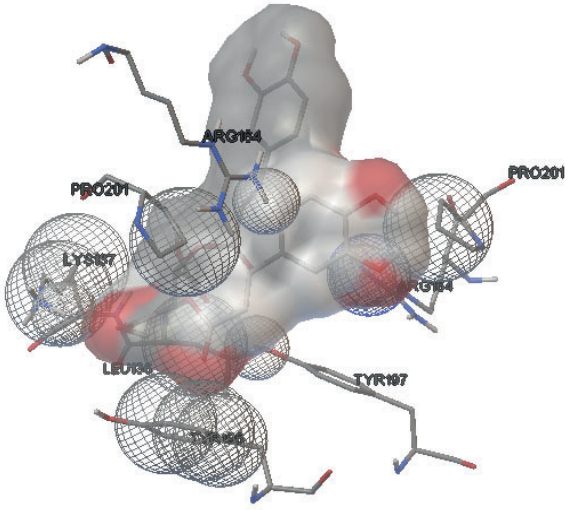

Figure 5: Illustrating the Interaction of Docked Protein and Ligand Complex.

pdbqt file which was then used to proceed with the visualization and analysis process.

3.5. Data Analysis

The analysis complex formed with the most negative binding energy was analyzed using BIOVIA Drug Discovery Studio. Figure 6 below shows the precise interaction between the amino acids of the protein and the ligand molecule. To get a clear idea of the types of bonds involved in the formation of a stable complex, the two-dimensional structure was constructed as illustrated in Figure 7. The amino acids involved in the formation of complex involved LYS137, ARG164, CYS264, GLY125, LYS137, GLU124, TYR195, and PRO201 (Table 1).

4. RESULTS AND DISCUSSION

The binding free energy is calculated by summing the interaction energies for polar, non-polar, and non-bonded interactions. Final total internal energy, total intermolecular energy, and torsion-free energy must all be summed up to determine binding energy. This energy is then subtracted from the energy of an unbound system. The docking findings and a list of the binding energies were acquired from the DLG file format. There is a general rule that the more negative binding energy there is, the more stable the protein and ligand complex is. The selected ligand "Chicoric acid" and receptor/ protein "caspase-3" generated a stable complex with a multitude of bond topologies, as determined by the computation of the bind-

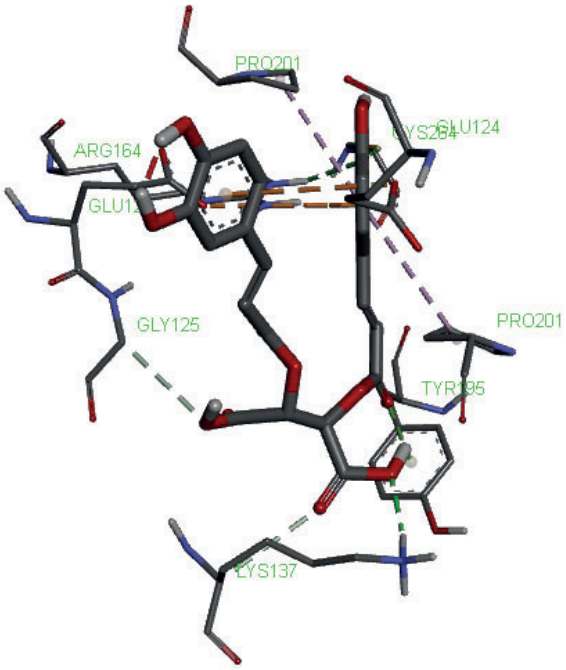

Figure 6: Illustrating the Ligand Molecule and the Amino Acids of Protein Involved in the Interaction.

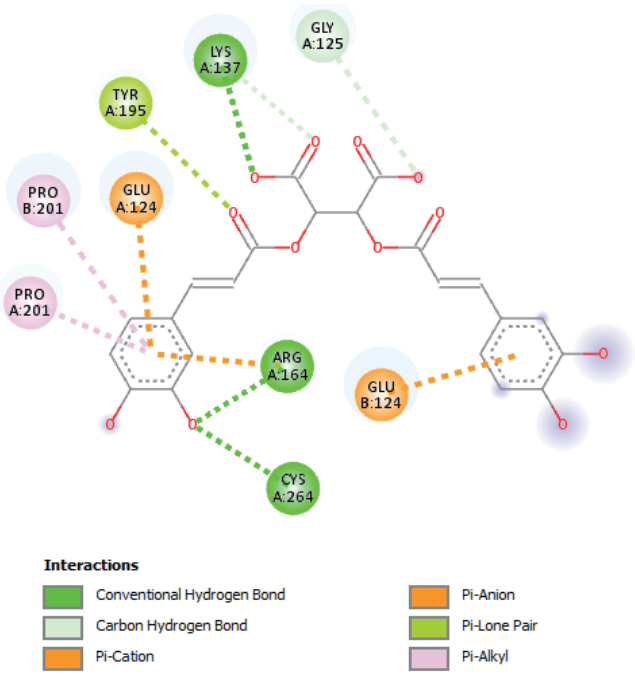

Figure 7: Illustrating the Two-Dimensional Docked Complex of Protein and Ligand.

Table 1
Enlisting the Distance, Bond Type Between Ligand and the Amino Acids of the Protein.

Ligand: Protein	Distance	Bond Category	Bond Type
UNL1 : LYS137	2.33985	Hydrogen Bond	Conventional Hydrogen Bond
UNL1 : ARG164	2.83672	Hydrogen Bond	Conventional Hydrogen Bond
UNL1 : CYS264	3.36835	Hydrogen Bond	Conventional Hydrogen Bond
UNL1 : GLY125	3.69528	Hydrogen Bond	Carbon Hydrogen Bond
UNL1 : LYS137	3.58631	Hydrogen Bond	Carbon Hydrogen Bond
UNL1 : ARG164	3.85478	Electrostatic	Pi-Cation
UNL1 : GLU124	4.64832	Electrostatic	Pi-Anion
UNL1 : GLU124	4.6282	Electrostatic	Pi-Anion
UNL1 : TYR195	2.84421	Other	Pi-Lone Pair
UNL1 : PRO201	5.20423	Hydrophobic	Pi-Alkyl
UNL1 : PRO201	5.37965	Hydrophobic	Pi-Alkyl

ing energy. The binding energy of this complex was -15.46 kcal/mol.

5. CONCLUSION

One of the most important socioeconomic concerns nowadays is cardiovascular disease. Changes in lifestyle, especially dietary habits, are essential for preventing cardiovascular disease. Apart from the modifiable risk factors, there are an increasing number of side effects attributed to the medications and synthetic drugs employed to manage heart disease. Therefore, studies are now being conducted to look for an alternative that can be a phytocompound. The present study explored the targeting ability of a phytocompound against the emerging target protein of heart failure called caspase-3. The results revealed promising inhibition as demonstrated by negative binding energy. However, the limitation of the present study is that there is a need for large In Vivo and In Vitro studies to confirm the findings.

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