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Computational Design for Human Angiotensin Converting Enzyme as a Target for Arjunolic Acid Causes Coronary Artery Disease

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Abstract

A leading cause of mortality around the globe is coronary artery disease (CAD). Major improvements in CAD therapy have been developed during the last ten years. According to the degree, kind, and clinical manifestation of CAD, the current treatments are either chemical treatments, surgical, or a combination of both. The bark of the Indian medicinal plant "Terminalia arjuna" has been used for decades as a heart stimulant. Several medicinal elements, including saponins and flavonoids, have been isolated from the bark. Terminalia arjuna has been the subject of numerous experimental and clinical research for its ability to treat cardiovascular diseases. Because protein-ligand interactions are important in structure-based treatment discovery, we used molecular docking to analyze Arjunolic acid (phytochemical found in T. arjuna) and examined their binding affinity against the cardiovascular target protein. The three-dimensional (3D) structure of the Human Angiotensin Converting Enzyme (Target Cardiovascular Protein) was obtained from Protein Data Bank and docked using the Autodock tool. As a result of our research, T. arjuna seems to be a good option for producing broad-spectrum medicines to treat cardiovascular disease.

Keywords

Arjunolic Acid, Autodock, Coronary Artery Disease (CAD), Human Angiotensin Converting Enzyme, Protein Data Bank (PDB), Terminalia arjuna

Imprint

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1. INTRODUCTION

Atherosclerotic plaque growth in the lumen of a blood vessel, a condition called coronary artery disease (CAD), reduces blood flow and oxygen to the heart muscle. The development of atherosclerosis in the coronary arteries is diagnostic of CAD, which causes arterial lumen obstruction and, ultimately, myocardial ischemia, hypoxia, and necrosis. The American Heart Association estimated in their 2016 report on stroke and cardiovascular disease CHD prevalence rates in the United States showed that 15.5 million individuals were affected [1]. As a result, CHD is linked with a large social and economic burden, in addition to its devastating impact on a patient's life quality. The need to find alternative therapeutic techniques with a lower risk of adverse effects is further emphasized by the fact that utilization of aspirin, statins, and other drugs for an extended period, might have negative consequences on health [2].

The most frequent kind of cardiac illness is coronary artery disease. Atheromatous alterations in the coronary blood arteries are to blame. From asymptomatic atherosclerosis and moderate angina to acute coronary syndrome, all of these diseases are included under the umbrella term "coronary artery disease". It remains a major illness in the United States. The first step in preventing coronary artery disorders is to evaluate possible risk factors [3].

The percentage of 2016 fatalities in India attributable to cardiovascular illnesses is shown below. One-third of all fatalities in the nation were caused by cardiovascular disease. Ischaemic heart disease accounted for 17.8 percent of all fatalities in this category throughout the study period shown in Figure 1. Chronic inflammation is widely believed to be a cause of heart disease and stroke, from the development of the fatty streak through the progression to a fibrous atheroma [4]. Endothelial dysfunction is the catalyst for this process. Many different things, including but

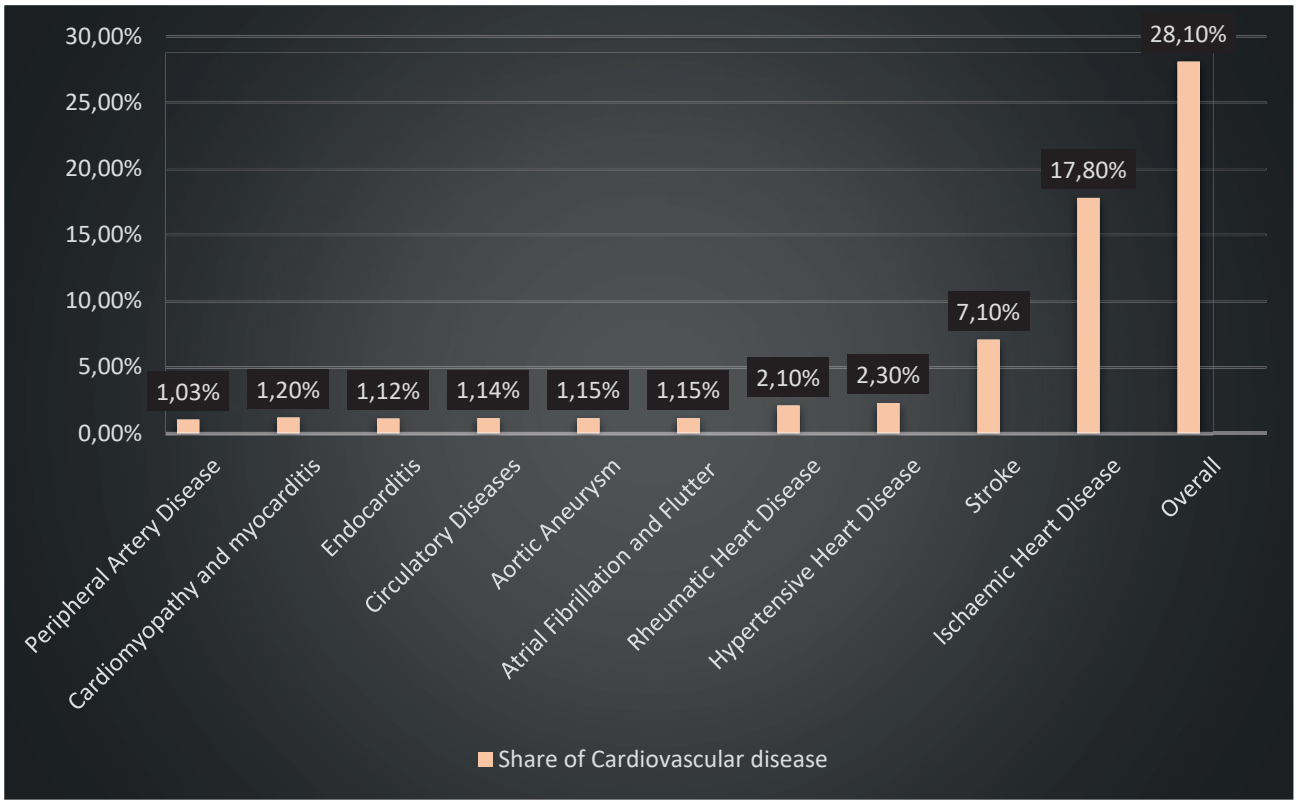

Figure 1: Shows the Deaths in India attributable to cardiovascular illnesses in 2016.

not limited to, extreme stress, oxidative harm from free radicals, genetic modifications, persistent infection, and elevated cholesterol, may contribute to this condition. Untreated high blood pressure, diabetes, smoking, and maybe even genetics have all been linked to this phenomenon [5].

Endothelium produces inflammatory cytokines in response to an initial injury and becomes extremely responsive to leukocytes, particularly monocytes and platelets. The endothelium acts as a magnet for monocytes, which then develop into macrophages and consume the oxidized low-density lipoprotein (LDL) particles, resulting in the formation of lipid-laden foaming macrophages [6]. A fibrous atheroma is formed when smooth muscles migrate and proliferate in response to chronic inflammation. Fibrous atheromas have an oxidized lipid area covered by macrophages and necrotic tissue and a collagen-rich substrate and regenerative smooth muscle.

The gold standard of care for those with congestive cardiac failure or coronary artery disease with the malfunction of the "left ventricle (LV)" is "Angiotensin-Converting Enzyme (ACE)" inhibitors. By catalyzing the breakdown of angiotensin II, angiotensin-converting enzyme 2 (ACE2) contributes to the maintenance of normal renin-angiotensin system function [7]. Biomarker screenings, including those for circulating ACE2, will likely compete for scarce healthcare resources, with only the most effective tools being used in primary care. In this setting, only the most economical biomarkers that can be used to develop therapies to mitigate the effects of cardiovascular disease will be able to compete. To determine whether or not measuring plasma ACE2 is more cost-effective than current clinical practices, a cost-utility analysis should be conducted (QALY) [8]. Using quality-adjusted life years "(QALYs)" as a metric, researchers can evaluate the value of biomarkers is anticipated to be lower than that of direct therapies, making this sort of study all the more crucial [9].

These days, researchers are looking into the medicinal potential of promising new compounds, particularly those produced from natural resources since they are harmless to people and may be found in meals. There have been lengthy accounts of the successful therapeutic use of several plants. These antioxidant-rich herbs have a major part in Ayurvedic medicine's treatment of heart disease or other issues. Protecting cells and tissues from harmful free radicals like ROS, antioxidant bioactive molecules are required. Most chemicals of this class have properties with both antioxidants and signaling molecules facilitate or control the initiation or progression of a signaling or regulatory sequence that leads to physiological changes and gene expression, these chemical's signal transduction pathways are regu-

lated by proteins that interact with other critical cellular proteins (usually kinases and enzymes).

Drugs that block the action of the enzyme angiotensin-converting are among the most effective treatments available. "Captopril", "Lisinopril", "Enalapril", and "Ramipril" are just a few examples of drugs that work as ACE inhibitors. Side effects include dizziness, coughing, and angioneurotic edema may not appear until the medications have been used for an extended period. There has been substantial research into potential new medication replacements for these medicines. Bioactive chemicals derived from natural sources have been the primary focus of most studies. The effects of Hibiscus sabdariffa anthocyanins on ACE inhibition were investigated. Natural glycosides were shown to block ACE activity, as reported by Charles *et al.* [10] aglycone forms of those other flavonoid glycosides, such as quercetin, may be found in foods including citrus fruits, wheat, and onions. When rhamnose and rutinose are added to quercetin, the glycosides quercitrin and rutin are produced [10].

"Arjunolic acid", a chiral "*triterpenoid saponin*", was isolated from "*T. arjuna*" bark. Its chemical name is "2, 3, 23-trihydroxyolean-12-en-28-oic acid". It has a wide range of biological effects, including those that fight diabetes, fungus, bacteria, cholinesterase, tumors, and asthma, and are well known as shown in Figure 2. Arjunolic acid's antioxidant properties are widely linked to its ability to neutralize oxygen-derived free radicals. Arjunolic acid's antioxidant capabilities result from its ability to donate hydrogen atoms, chelate metal ions, and stabilize carboxyl radicals via resonance [11].

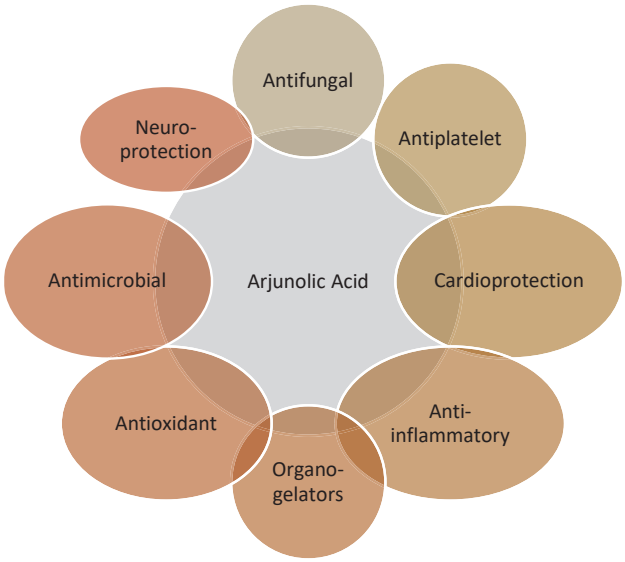

Figure 2: Illustrated the Arjunolic acid participates in a wide variety of biological processes.

2. LITERATURE REVIEW

Syed Aun Muhammad and Nighat Fatima stated in their study to use computational docking studies to examine the inhibitory impact of quercetin glycosides. "Angiotensin-converting enzyme (ACE; peptidyl-dipeptidase A)" the crystal structure was derived from the Protein Data Bank (PDB) (PDB ID: 1O86). The commonly used "ACE inhibitor" enalapril was used as the gold standard in this study. This study used PyRx with the AutoDock Vina capability to conduct a scoring-function-based computational docking analysis. Using the reference value of the gold standard (7.0 kcal/mol), quercetin's binding energy with its molecular target (angiotensin-converting-enzyme) was much lower. Based on these findings, quercetin glycosides deserve further investigation as a possible ligand use in treating high blood pressure, heart attacks, and other cardiovascular issues [12].

Navjot Kaur *et al.* evaluated the *Terminalia arjuna* efficacy for those who suffer from chronic stable angina. Select. In those with chronic stable angina, they evaluated a commercial preparation of Terminalia arjuna to conventional or standard treatment. The author's meta-analysis failed to find any differences between the "*Terminalia arjuna*" group and also the control arm due to methodological flaws in the original studies. Finally, in chronic stable angina patients, the data is inadequate to support or disprove "*Terminalia arjuna*". To determine Terminalia arjuna's medicinal efficacy, well-controlled multicentric clinical studies must be done on a large number of individuals [13].

Patrick W. Serruys *et al.* conducted a study that although "Coronary-Artery Bypass Grafting (CABG)" has traditionally been the "percutaneous coronary intervention (PCI)" with drug-eluting stents is increasingly employed as standard therapy for coronary heart disease. An estimated 1800 patients with three-vessel or left main CAD had "CABG" or "PCI" "(1:1 ratio)". Local cardiac surgeons and interventional cardiologists discovered that both treatments might produce equal anatomical revascularization. Both groups had comparable preoperative features. Compared to the CABG group, the PCI group had a higher incidence of serious adverse cardiac or cerebrovascular incidents at 12 months "(17.8% vs. 12.4%; P = 0.002)", mostly because of a higher incidence of repeat revascularization "(13.5% vs. 5.9%; P = 0.001)". The goal of noninferiority was not met. Three-vessel or left main CAD patients are treated mostly with CABG since it reduc-

es negative cardiac or cerebrovascular results within a year [14].

3. METHODOLOGY

3.1. Design

Using the use of data mining and a comprehensive examination of the current literature, we were able to determine the most likely and effective ligand structure for treating coronary artery disease (CAD) with complementary and alternative therapies. In this work, the targeting potential of certain ligands and target proteins is investigated using a computational method and docking procedure. Data mining and a thorough examination of the existing literature led to the identification of Human Angiotensin Converting Enzyme as a protein of interest in the treatment of coronary artery disease (CAD) and Arjunolic acid as a chemical with this effect. After retrieving the protein and chemical from their respective databases, they were prepped for docking using Autodock4, and finally, the complex was visualized using BIOVIA Drug Discovery Studio (Figure 3).

3.2. Instrumentation:

Protein Data Bank (RCSB) and also the PubChem Chemical Database are accessed for ligand and protein structures, respectively. The "Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB)" in the United States serves as the data center for the international PDB database, and all users, including structural biologists, computational biologists, and others, have full access to the PDB data preserved by RCSB PDB. It keeps track of the three-dimensional shapes of proteins and nucleic acids, two of the most crucial building blocks of life. Biochemists and biologists from all over the world provide data, and techniques including "NMR spectroscopy", "cryo-electron microscopy", and "X-ray crystallography" are frequently used.

PubChem is an online database of chemicals and their biological assay activities. The system is ad-

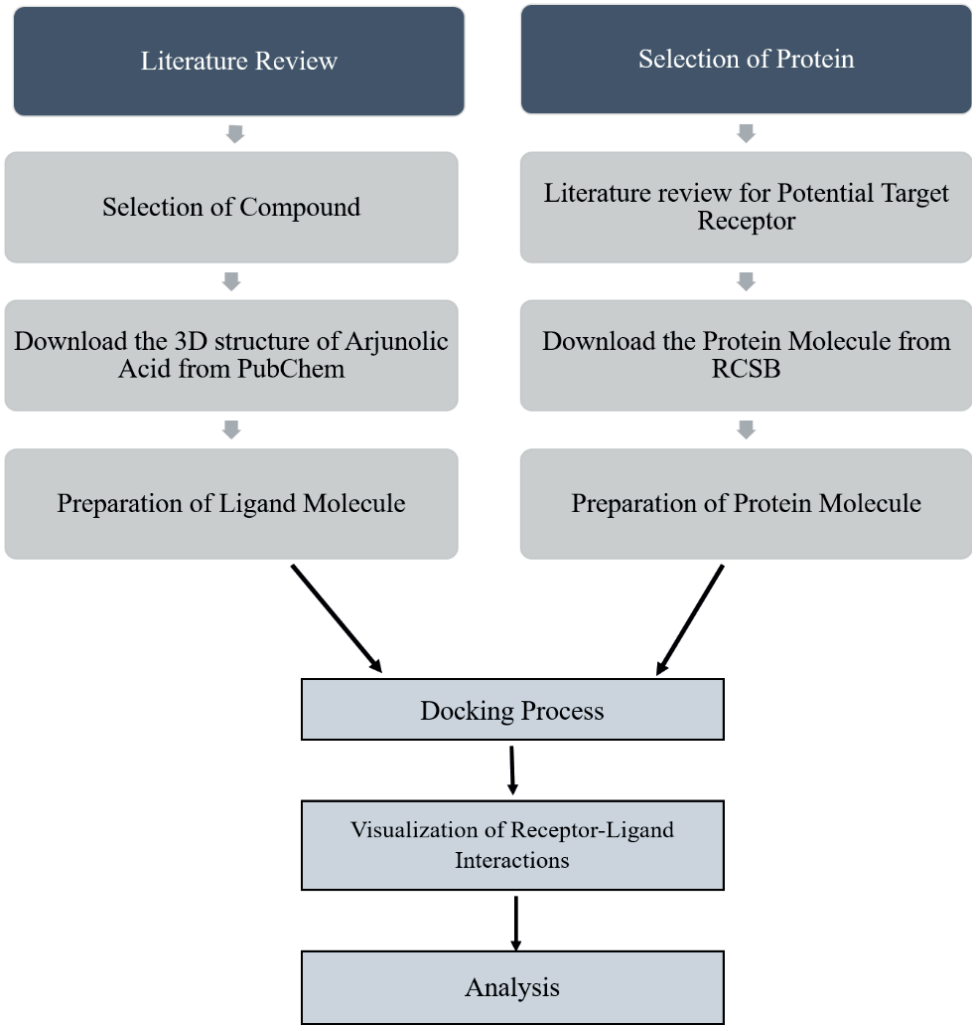

Figure 3: Illustrates the Procedures Utilized in the Study to Obtain the Docked Complex of Ligand and Protein.

ministered by the NCBI at the National Institutes of Health. When you think about the National Library of Medicine, what comes to mind is the National Center for Biotechnology Information. You may access PubChem using a web interface at no cost. The chemical structures and descriptions of millions of substances are accessible for free download through FTP. Compounds having fewer than 100 atoms and fewer than 1,000 bonds are among the many types of substances described in PubChem. The PubChem database has grown rapidly thanks to the contributions of more than 80 different database providers.

Autodock 4, among the most programs in the scientific literature, was utilized for the docking studies procedure. Using a docked log file, the software predicts how a chemical or ligand would attach to a protein or receptor in a real biological system. This information is then evaluated using a graphical program named BIOVIA drug discovery studio.

3.3. Sample

Most patients with heart failure, acute coronary syndrome nephrotic syndrome, hyperglycemia, or hypertension will benefit from therapy with an angiotensin-converting enzyme inhibitor (ACEI). It's worth noting that these inhibitors were created before the structure of the human ACE was known; rather, they were constructed based on a presumed mechanistic similarity using carboxypeptidase A. In light of this, we present the 2.0 X-ray structural of ACE to bound the frequently prescribed medicine lisinopril "(N2-[(S)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline; also sold as Zestril and Prinivil)". Anti-angiotensin-converting enzyme drugs lowered mortality and major cardiovascular event rates in individuals with coronary artery disease who did not have heart failure or decreased left ventricular function (Figure 4).

Ayurvedic medicine makes extensive use of antioxidant-rich herbal plants for the treatment of cardiovascular and other conditions. One such innovative phytomedicine with several therapeutic uses is *Arjunolic Acid*. *Terminalia Arjuna* was the first plant from which this triterpenoid Saponin was isolated; subsequent sources include *Combretum nelsonii,* Leandra chaeton, etc. One of the most effective antioxidants and free radical scavengers is arjunolic acid. Arjunolic acid has several beneficial effects that support its use as a cardiotonic in the Ayurvedic system of medicine, including protection against myocardial necrosis, platelet activation and coagulation, and reductions in blood pressure, heart rate, and cholesterol. Taken alongside vasodilators and diuretics, arjuna bark powder alleviates the symptoms associated with heart failure. Animal studies have shown that Arjuna bark treatment lowers decreases "total cholesterol and low-density lipoprotein (LDL)" cholesterol while increasing good-for-you "high-density lipoprotein (HDL)" cholesterol. The atomic and molecular composition of *Terminalia arjuna* (Arjunolic Acid) is shown in Figure 5.

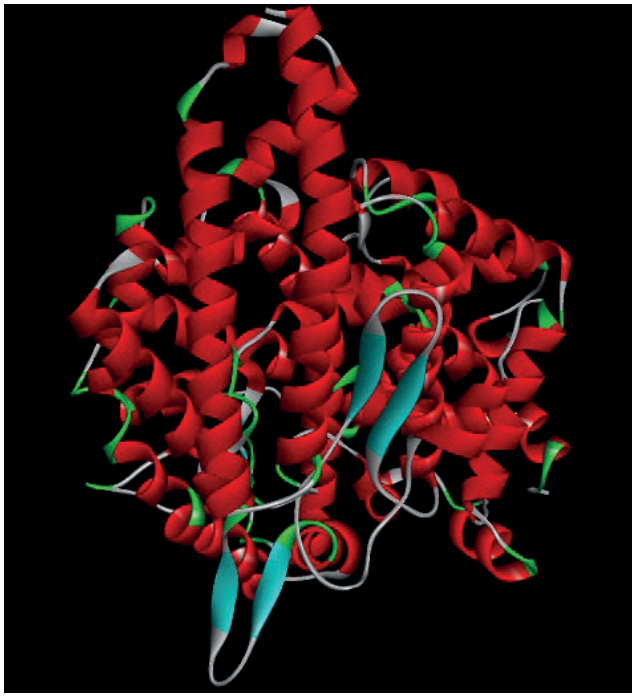

Figure 4: Shows a PDB (108A) based homology model of the crystalline structure of the human angiotensin-converting enzyme.

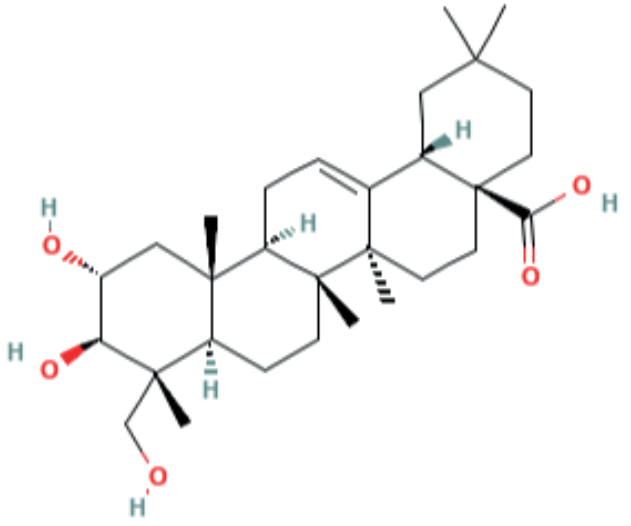

Figure 5: Displays the Chemical Structure of Terminalia arjuna (Arjunolic Acid).

The 2D structure *Terminalia arjuna* (Arjunolic Acid) is displayed in Figure 6. It has been noticed by researchers that patients in a variety of therapeutic contexts (for example, cancer and hypertension) Utilize complementary and alternative medicine (CAM) to a large extent (CAM). Furthermore, the majority of them are not backed by any clinical studies. Terminalia arjuna is a plant that is often used in traditional medicine. It is also known as "Arjuna", "Indradru", "Dhavala", "Nadisarja", "Kakubha", "Partha" and "Veeravriksha". Researchers in India have attempted to determine whether or not the plant is effective and whether or not it is safe. It is a huge tree that has evergreen leaves and is a member of the Combretaceae family. It may be found growing in abundance throughout India.

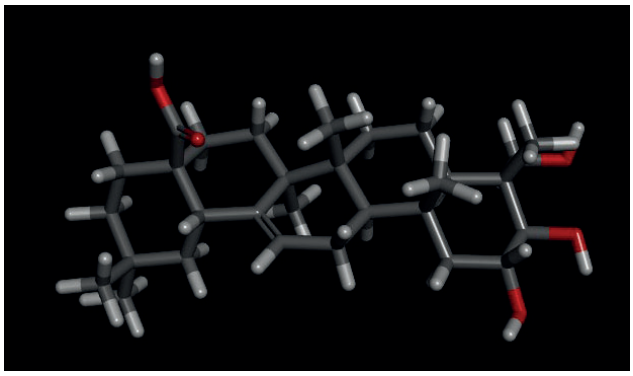

Figure 6: Displays the 2D structure of Terminalia arjuna (Arjunolic Acid).

3.4. Data Collection:

Numerous confirmations and sites for efficient interaction between the protein and ligand are generated by docking. As part of the docking procedure, the. gpf file was used to launch the auto grid and the. dpf file was used to launch autodock4. To carry out the docking, a protein or macromolecule was made stiff and the ligand was made flexible. The DLG file's binding energy for various docked confirmations was obtained using the autodock tool. As shown in Figure 7, the confirmation with the largest negative binding energy was utilized to depict the interaction, and this was followed by the creation of a complex.pdbqt file for further analyses and visualization.

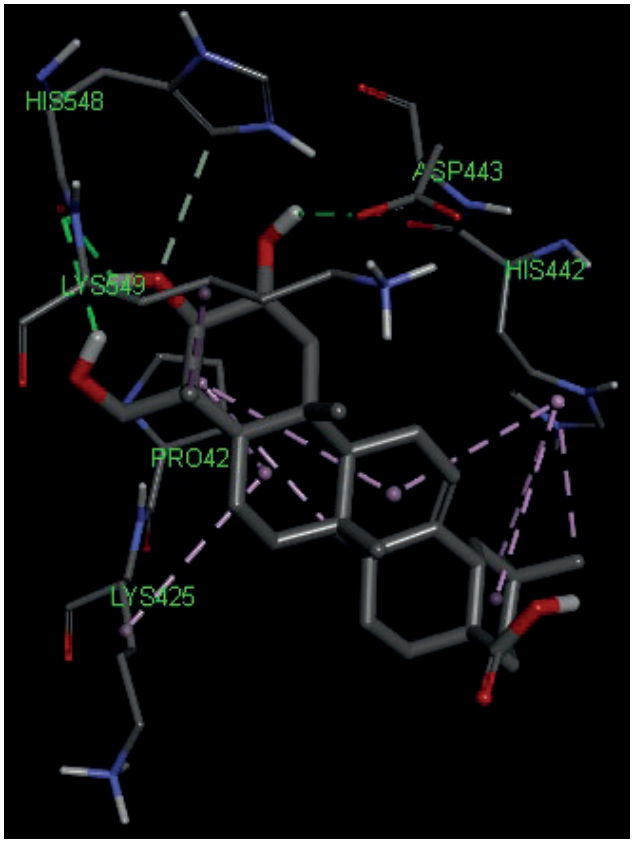

Figure 7: Shows the Interactions Between the Docked Protein and the Ligand Complex.

3.5. Data Analysis:

The binding energy of the complex generated was calculated using BIOVIA Drug Discovery Studio, and the one with the lowest value was chosen for further study. The particular characteristics of the interactions that take place between the amino acids of the protein and the ligand molecule are seen in Figure 8 below. The two-dimensional structure was built according to the recommendations in Table 1 to acquire a clear picture of the many kinds of bonds involved in the creation of a stable complex.

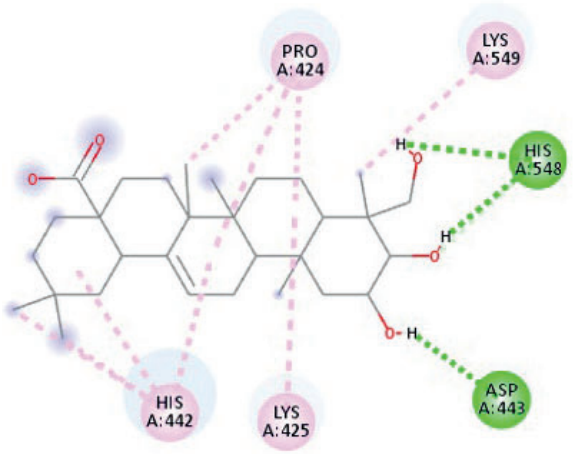

Figure 8: Illustration of The Protein Amino Acids and Ligand Molecular Interaction.

4. RESULTS AND DISCUSSION

It is possible to determine the binding free energy by adding the energies of polar, non-polar, and non-bonded interactions. To calculate binding energy, one must add the final values for internal energy, intermolecular energy, and torsion-free energy. When cal-

Table 1

Displays the types of bonds formed between the protein and the compounds.

Amino Acids	Bond Length	Type of Bonds
UNL1-HIS548	2.82829	Hydrogen bond
UNL1-HIS548	2.15027	Hydrogen bond
UNL1-ASP443	2.05398	Hydrogen bond
UNL1-HIS548	3.40118	Hydrogen bond
UNL1-PRO424	5.26902	Hydrophobic
UNL1-PRO424	4.1162	Hydrophobic
UNL1-LYS425	4.53047	Hydrophobic
UNL1-PRO424	4.5118	Hydrophobic
UNL1-LYS549	3.2131	Hydrophobic
UNL1-HIS442	5.24106	Hydrophobic
UNL1-HIS442	4.76886	Hydrophobic
UNL1:C-HIS442	3.84511	Hydrophobic
UNL1:C-HIS442	4.74764	Hydrophobic

culating the total energy of an unconstrained system, this energy is deducted. The DLG file format was used to get the docking results and a catalog of binding energies. The stability of the protein-ligand combination increases as the binding energy decreases. The binding energy calculation showed that the combination of the ligand "Arjunolic acid" and the receptor/protein "Human Angiotensin Converting Enzyme (108A)" produced a stable complex with a wide variety of bond topologies shown in Figure 9. This compound has a binding energy of -6.49 kcal/mol.

5. CONCLUSION

CAD remains a significant morbidity and mortality contributor despite medical advancements in cardiovascular research. Researchers, doctors, and other professionals have developed varied and inventive approaches to cure CAD and also its related disorders. Some of these approaches have solid evidence for therapeutic use, while others are currently under investigation. The docking values and examination of the compounds' interactions indicate that the compounds of T. Arujna have the capability of binding to several targets implicated in cardiovascular disease. This research found that Arjunolic acid might be utilized as a possible treatment for cardiovascular disease. Despite just having early information on certain revolutionary therapeutic procedures, the results are promising and might become future treatment possibilities.

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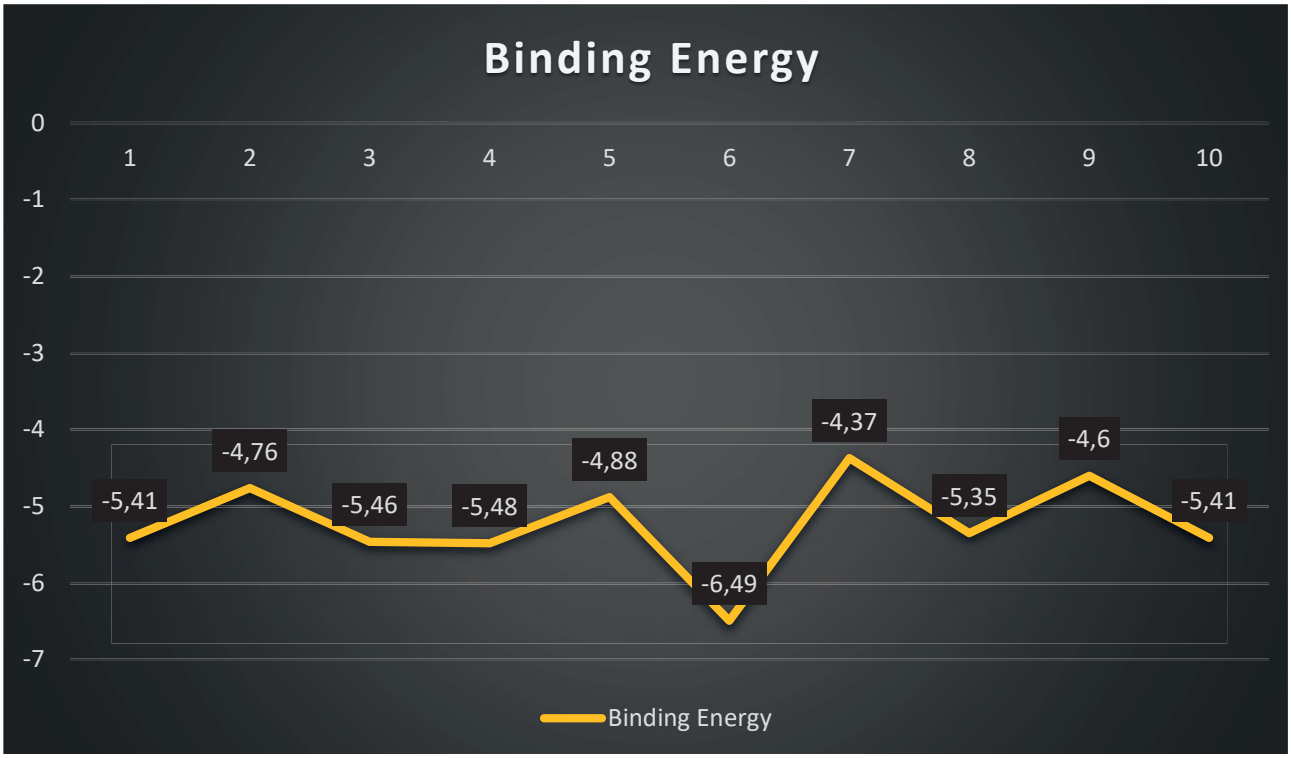

Figure 9: Representing the Binding Energy of Different Conformational Clusters.

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