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Original Article

Network Pharmacology and Molecular Docking Study to Reveal the Underlying Mechanism of (*Arjuna*) *Terminalia arjuna* (Roxb.) Wight and arn. In the Management of Coronary Heart Disease

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ABSTRACT

Background: Atherosclerosis narrows the coronary arteries, causing Coronary Artery Disease (CAD), a leading cause of morbidity and death worldwide. Conventional treatments typically focus on individual targets or pathways, which may not sufficiently address the complex and multivariate nature of CAD. Ayurvedic medicine has made extensive use of *Terminalia arjuna* (Arjuna), a traditional herbal remedy with cardioprotective qualities, to treat CAD. We used network pharmacology in conjunction with molecular docking techniques to obtain a thorough grasp of how multiple phytoconstituents in Arjuna collectively exert positive therapeutic effects on CAD. **Materials and Methods:** This study assessed through IMMPAT and Dr. Dukes databases, DisGeNET and GeneCards, PPI network diagram construction and analysis, KEGG enrichment analysis, three networks we built and analysed, the link between the main chemical and *Arjuna's* primary targets was examined through molecular docking technique. **Results:** Through this approach, we identified five core bioactive compounds-Ellagic Acid, Leucodelphinidin, Arjungenin, Quercetin, and Arjunglucoside I-and five key target proteins-SRC, EGFR, ESR1, ERBB2, and JUN. Subsequent common-target enrichment analysis revealed that the main pathways modulated by *Arjuna* include insulin resistance, adherens junction and RAP1 signaling pathways. Molecular docking further confirmed strong interactions between the core compounds and the active sites of these targets, reflected by favorable docking scores. **Conclusion:** This study elucidates the molecular and pharmacological mechanisms by which Arjuna exerts its therapeutic effects against coronary artery disease. While additional preclinical and clinical research on these compounds is necessary to develop a potential therapeutic entity for the treatment of coronary artery disease.

Keywords: *Arjuna*, *Terminalia arjuna*, Coronary Artery Disease, Molecular Docking, Network Pharmacology.

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INTRODUCTION

Coronary Artery Disease (CAD) is defined by the accumulation of atherosclerotic plaque in the arterial lumen (Ralapanawa *et al.*, 2021). This heart condition impairs blood flow, which lowers the amount of oxygen that reaches the myocardium (Dalen JE *et al.*, 2014). Globally, CAD is the leading cause of significant morbidity and mortality. Based on estimates over the past few decades, the prevalence of CAD in India has ranged between 1.6% and 7.4% in rural areas and between 1% and 13.2% in urban areas (WHO 2025). In addition to its detrimental impact on patients' quality of life, CAD imposes a substantial societal and financial burden. Long-term usage of statins, aspirin, and other medications is part of the conventional treatment regimen of CAD, which can have negative health effects (White AA *et al.*, 2011; Wood FA *et al.*, 2020). For this reason, new therapeutic approaches with a lower risk of side effects must be found. Therefore, expanding clinical care resources-especially those derived from natural resources like plants-remains essential. Even while Ayurveda did not envision the circulatory system in the manner that modern medicine does, it seems that the numerous allusions to cardiovascular activity suggest that the ancient Acharyas shared a similar understanding (Nishteswar K 2014). Ayurvedic literature documented many drugs employed in Hridroga (heart disease) and attributed the term Hrudya (conducive to heart health)

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to Arjuna (*Terminalia arjuna* (Roxb.) Wight & Arn) (Prabir N *et al.,* 2024). A thorough examination of this herbal remedy used to treat hridroga (heart disease) makes it abundantly evident that it has anti-platelet, thrombolytic, hypotensive, and hypo-cholesterolemic properties—all of which are essential for the treatment of CAD (Dwivedi *et al.,* 2014). However, neither the natural phytochemicals found in Arjuna nor their mechanisms of action against CAD have been thoroughly studied. Its bioactive chemical components' molecular mechanism in particular needs more research. Therefore, the main objective of this study was to use network pharmacology and molecular docking to investigate the biological pathways, active chemicals, and possible targets of the Arjuna. This could serve as a foundation for future research and clinical applications.

MATERIALS AND METHODS

Bioactive compound screening of *Arjuna* and collection of disease target pertaining to bioactive compounds

The phytochemical dataset of *Arjuna* was gathered using the IMMPAT (Vivek Ananth *et al.,* 2023) and Dr. Dukes (Lans C *et al.,* 2020) databases as well as a literature review. The Swiss ADME (Dalen JE *et al.,* 2014) and Pubchem (Kim S *et al.,* 2025) databases were used to screen the acquired phytochemical dataset for ADME characteristics. The bioactive phytochemicals found in *Arjuna* were screened using the Lipinski violation ≤ 1 and the bioavailability score > 0.55. Swiss Target Prediction (Diana A *et al.,* 2019) and Binding DB (Gilson MK *et al.,* 2015) were used to find targets linked to *Arjuna*.

Collection of targets associated with CAD pathogenesis and obtaining overlapping targets

Data was gathered from the DisGeNET (Pinero J *et al.,* 2019) and GeneCards (Stelzer G *et al.,* 2016) regarding target genes linked to coronary artery disease. Using the search term "coronary artery disease," only proteins from Homo sapiens were chosen. The distributional results of CAD targets and target pertaining to *Arjuna* bioactive compounds were presented as Venn diagrams using online Venny tool 2.0.

Protein-Protein Interaction (PPI) network diagram construction and analysis

The association between overlapping targets related to *Arjuna* bioactive chemicals and CAD—which were thought to be possible therapeutic targets—was evaluated using the STRING database (Szklarczyk D *et al.,* 2022). The following criteria were selected to build the PPI network of possible therapeutic targets: "Homo sapiens" was the selected species and "high confidence of≥ 0.7" was kept as the degree of confidence. The PPI network was then examined with Cytoscape v3.7.2 software (Doncheva NT *et al.,* 2019) to determine the network's node topological metrics, such as degree value, Maximum Clique Centrality (MCC), and Maximum Neighbourhood Component (MNC). Thus, these three topology characteristics were used to choose the hub genes for the PPI network.

KEGG enrichment analysis

Overlapping targeted genes for core phytochemical in Arjuna were uploaded to the STRING database in order to identify the enriched pathways. A graphic representation of the top 10 modified KEGG pathways was provided, and the statistical filter value for the enrichment analysis was set at the 0.05 FDR cutoff.

Compound-target-pathway network construction of *Arjuna* against CAD

Following the addition of target genes, bioactive phytochemicals, and pathways, Cytoscape 3.7.2 software was used to create the network. The COMPOUND-TARGET-PATHWAY, PATHWAY-TARGET, and GENE-COMPOUND networks were the three networks we built and analysed. Topological examination was performed using the Network Analyser program. The primary CAD treatment targets and *Arjuna's* primary phytochemicals were identified based on degree.

Validation by molecular docking

Using a molecular docking technique, the link between the main chemical and *Arjuna's* primary targets was examined. The core compound's three-dimensional structure was retrieved via the PubChem database. The PDB database (Burley SK *et al.,* 2022) provided 3D structures of the key target, and we used the following criteria to choose the high-quality protein 3D structure: The organism of source is "Homo sapiens," with a refinement resolution of 2.5A. Water molecules were eliminated and polar bonds were added to the target protein using Biovia DS software. Later, molecular docking was implemented for assessing binding affinity using PyRx software (Dallakyan S *et al.,* 2014). Using the Biovia Discovery Studio program, the binding interaction with the highest docking scores has been presented in both two and three dimensions.

RESULTS

Bioactive compound screening of *Arjuna* and collection of disease target pertaining to bioactive compounds

Based on the literature analysis combined with database search, 47 phytochemicals were identified in *Arjuna*. The SwissADME database was used to assess the phytochemicals' pharmacokinetics parameter and 31 bioactive *Arjuna* components were selected based on the ADME criteria. Each active biocomponent's genes were obtained from BindingDB and Swiss target prediction. 191 genes were predicted to be targeted by 31 bioactive *Arjuna* components.

Collection of targets associated with CAD pathogenesis and obtaining overlapping targets

The GeneCard and DisGeNet databases yielded 10996 and 1709 putative targets of coronary artery disease respectively. After removing duplicates and incorporating CAD-related targets, 146 common targets were found through Venny, indicating possible overlaps between CAD-related targets and *Arjuna* bioactive compound targets.

Protein-Protein Interaction (PPI) network diagram construction and analysis

The STRING database was used to build the protein–protein–interaction network of 146 common genes. The PPI network was visualised in Cytoscape, wherein 146 nodes alongside 1249 edges were discovered. Three topological analysis techniques for hub gene estimation were examined using the CytoHubba plugin: the degree, Maximum Clique Centrality (MCC), and Maximum Neighbourhood Component (MNC). The genes that ranked highest were SRC, EGFR, STAT3, ERBB2, PIK3CA, ESR1, and JUN (Figure 1).

KEGG enrichment analysis

KEGG analysis extracted from String Database indicated that the key targets of *Arjuna* in the therapeutic management of CAD were enriched in EGFR pathway, Insulin resistance, Adherens Junction, Rap 1 signalling pathway, Age Rage signalling pathway. Figure displays the top ten paths found by the enrichment analysis (Figure 2).

A network of compound-target-pathways was built in order to more precisely identify *Arjuna's* mode of action in the therapy of CAD. 183 nodes and 559 edges make up the network, which is seen in Figure 3 and is made up of compounds, protein targets, and pathways. Quercetin, Ellagic Acid, Luteolin, Kaempferol, Cerasidin, Arjunetin, and Arjunglucoside II were among the key chemicals that emerged (Figure 4).

Validation by molecular docking

Using the hub gene estimation results, important targets were molecularly docked to the top 15 *Arjuna* core phytochemicals. As a measure of how strongly a protein binds to a ligand chemical, the binding energy can be used to assess the stability between the two. According to previous research, the more steady the binding conformation of the two and the greater the likelihood of interaction, the lower the binding energy of the ligand to the receptor. This is typically measured at −5 kcal/mol. According to the Table 1 data, 5 core chemicals were able to bind to 5 hub genes with a relatively high binding potential ranging -7 to -9 Kcal/mol^{-1}. The highest binding affinity is displayed in Figure 3.

DISCUSSION

Ayurveda practitioners frequently advocates Arjuna for hridroga (cardiovascular disorders). Several preparations of Arjuna stem bark have shown a wide range of pharmacological effects including inotropic, anti-ischemic, antioxidant, blood pressure-lowering, antiplatelet, hypolipidemic, antiatherogenic and antihypertrophic effects (Maulik SK *et al.,* 2012). Although it showing significant clinical improvements in the sittings of cardiovascular disorders but its exact molecular mechanism in treating coronary artery disease is unknown. The network pharmacology of Arjuna was undertaken to identify the exact mechanism involved in treating coronary artery disease. Current research indicates Ellagic Acid, Leucodelphinidin, Arjungenin, Quercetin, and Arjunglucoside I are the major active ingredients present in Arjuna that are responsible for the improvement in CAD. Earlier studies also signify promising results of ellagic acid in improving endothelial function, reduce oxidative stress, and stop vascular dysfunction their by in preventing Coronary Artery Disease (CAD) (Li. J *et al.,* 2013). It also regulates cholesterol metabolism and potentially has anti-inflammatory effects which suggests its role in enhancing overall cardiovascular health (Pei S *et al.,* 2022). The role of leucodelphinidin in lowering cholesterol in animals fed with a high-cholesterol diet has also been reported ("Hypolipidemic effect" 2025). This hypocholesterolemic effect of leucodelphinidin has positive implications as it prevents the formation of atherosclerotic plaques that occur due to elevated levels of cholesterol and their by preventing or treating CAD (Shah K *et al.,* 2014). Many preclinical studies in animal models have demonstrated the quercetin's ability to reduce the size of atherosclerotic plaques, prevent ischemia-reperfusion injury, and improve heart function in the sittings of post myocardial infarction (Patel RV *et al.,* 2018). Arjun glucoside I is reported to have a role in preventing the damage to the heart muscle, particularly in cases of reperfusion (blood flow restored after a blockage) or ischemia (low blood flow) (Amlraj A *et al.,* 2017). It also helps prevent plaque formation in the arteries, which is one of the primary causes of CAD (Kapoor D *et al.,* 2014). The study's findings imply, treatments that target important genes like SRC, EGFR, ESR1, ERBB2, and JUN may be responsible for Arjuna's beneficial effects in CAD patients. The c-Src gene influences multiple pathways related to vascular dysfunction, oxidative stress, and cell behavior, all of which significantly influence coronary artery disease, in particular when c-Src is activated, more Reactive Oxygen Species (ROS) are produced, which damage blood vessels, contributing to atherosclerosis, hypertension, and cardiac hypertrophy (Hussain M *et al.,* 2023). The Epidermal Growth Factor Receptor (EGFR) activation is specifically associated with endothelial dysfunction, neointimal hyperplasia, atherogenesis, and cardiac remodeling, signifies that its chronic dysregulation may contribute to development and course of Coronary Artery Disease (CAD) (Makki N *et al.,* 2013).

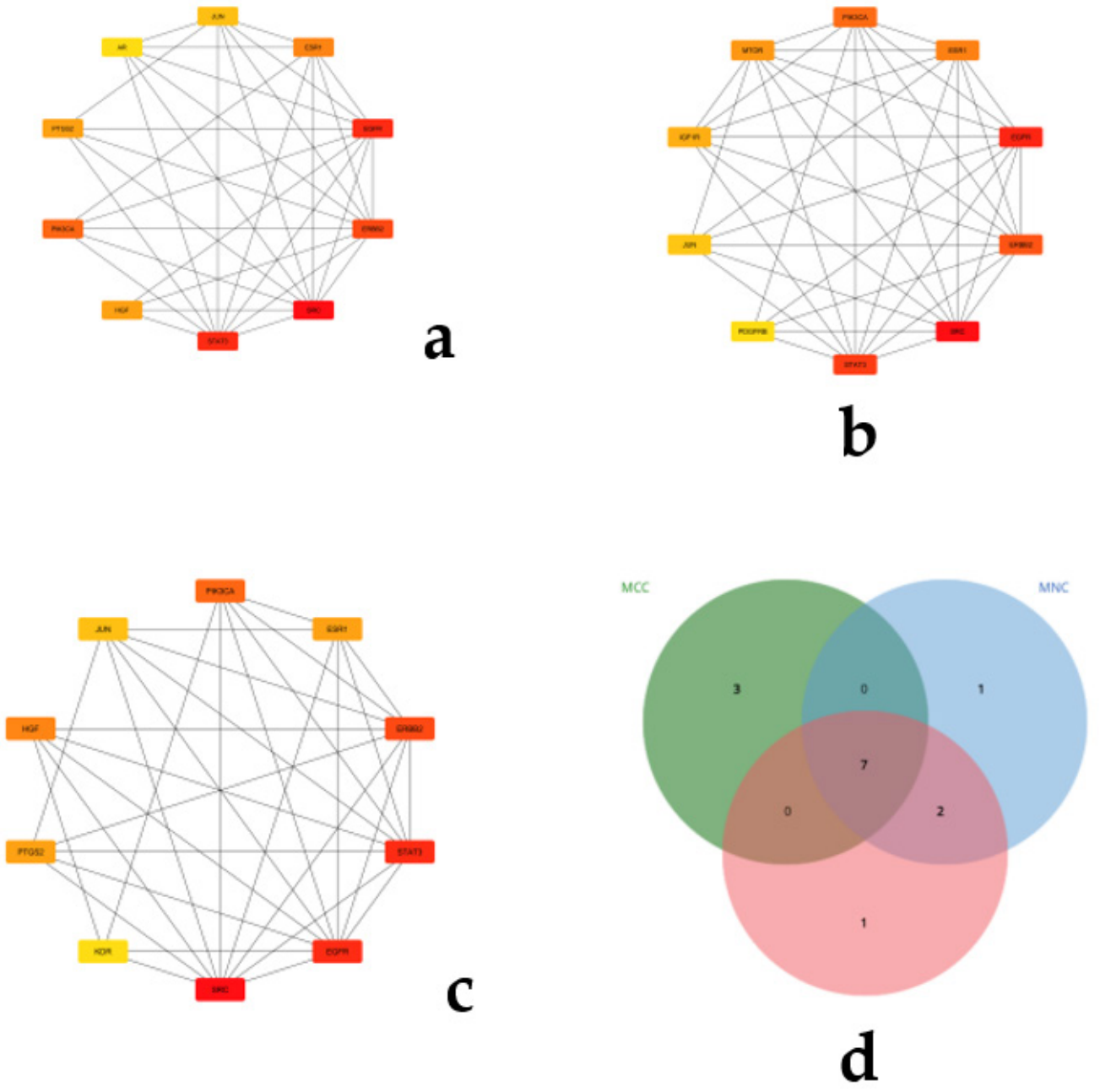

Figure 1: Top 7 Arjuna-CAD Hub gene prediction. Here (a) represent degree algorithm, (b) represent MCC algorithm, (c) represent MNC algorithm, (d) represents 7 hub genes after intersection of 3 algorithm output through Venn diagram.

ERBB2 (also known as HER2), is crucial for heart myocytes regeneration and preventing ischemic damage in coronary artery disease. (D'Uva G *et al.*, 2015) erb-b2 receptor tyrosine kinase when activated, promotes proliferation, differentiation and cardiomyocyte survival. Lower levels of ERBB2 are observed in patients with ischemic heart disease, suggesting the importance of this protein in maintaining heart health and preventing damage. (Gordon LI *et al.*, 2009). c-Jun affects the proliferation and inflammatory responses associated with atherosclerosis Coronary Artery Disease (CAD) by multiple pathways (Sozen E *et al.*, 2014). Specifically, the c-Jun and its associated Kinase (JNK) pathways influence the development of atherosclerotic plaques, heart failure, and myocardial damage (Baker AR *et al.*, 2008).

The ESR1, a gene that encodes the Estrogen Receptor alpha (ERα), which plays a role in the prevention of Coronary Artery Disease (CAD). Cells affected in atherosclerosis that include cardiac, smooth muscle, and endothelial cells showed a reduction in ERα express, signifying its role in the prevention

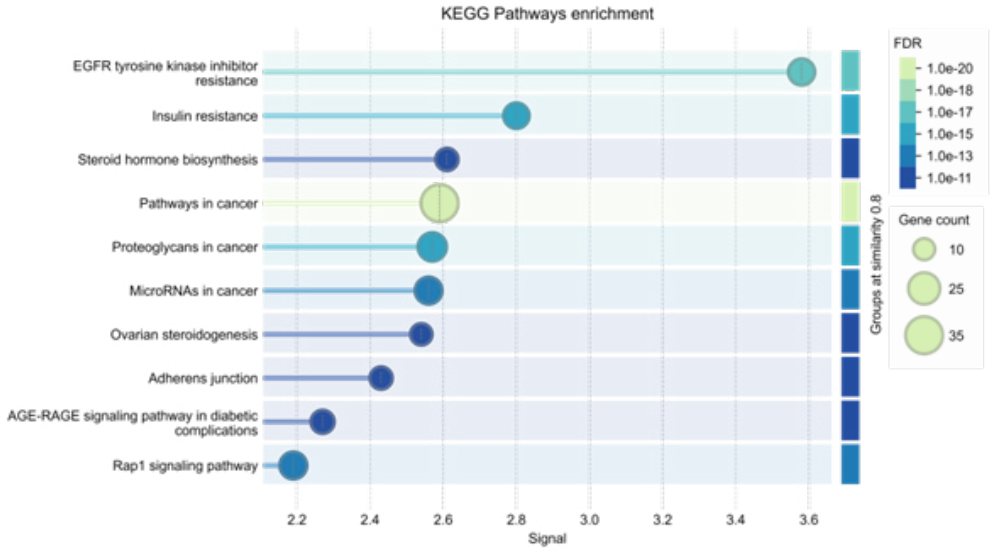

Figure 2: Top 10 KEGG enriched pathway bar chart obtained from STRING database Compound-target-pathway network construction of *Arjuna* against CAD.

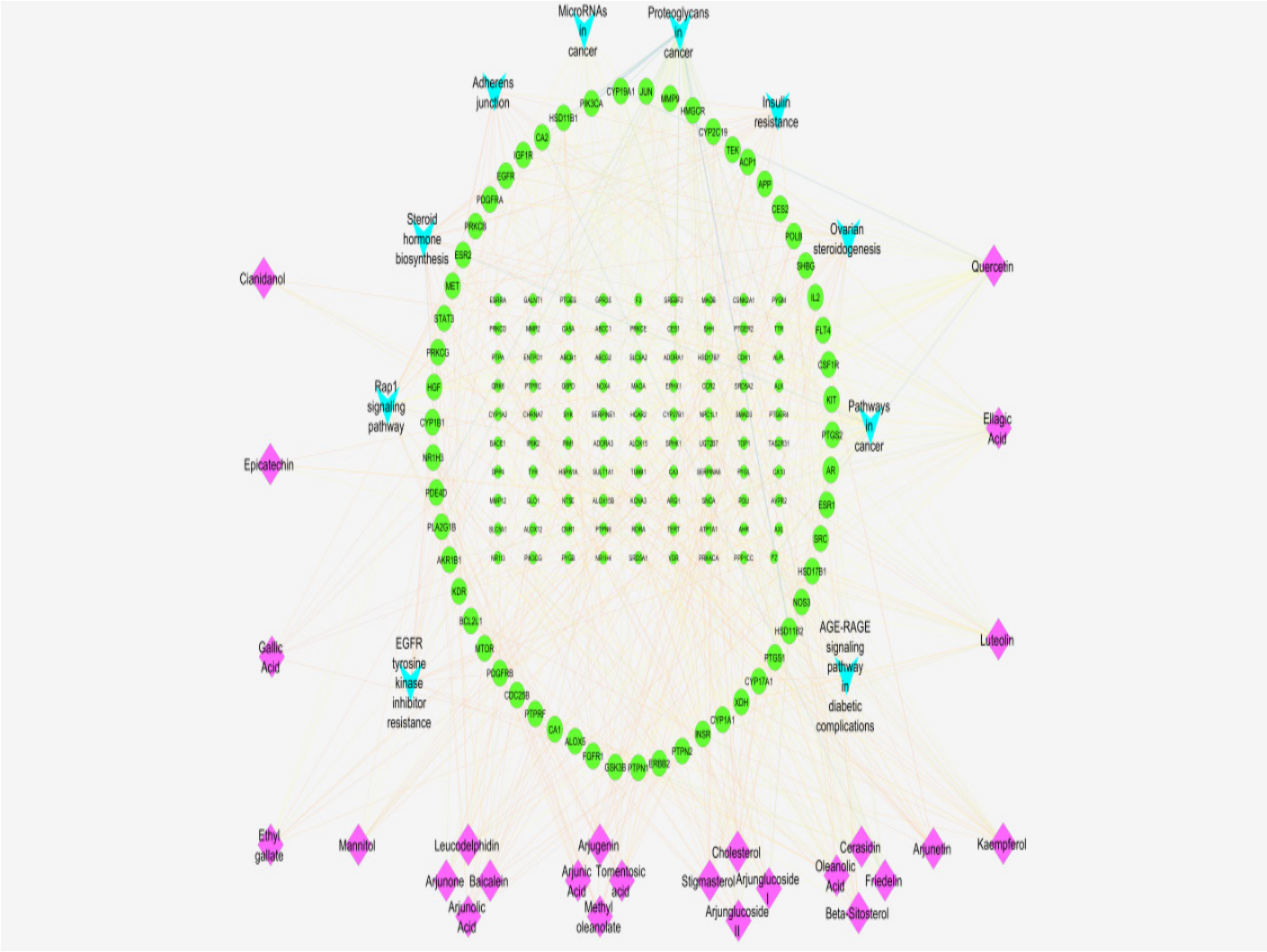

Figure 3: Binding interaction's visual depiction with the most significant docking scores (a : SRC-Ellagic Acid, b: EGFR-Leucodelphidin, c: ERBB2-Arjugenin, d: ESR1-Quercetin, e: JUN-Arjunglucoside I).

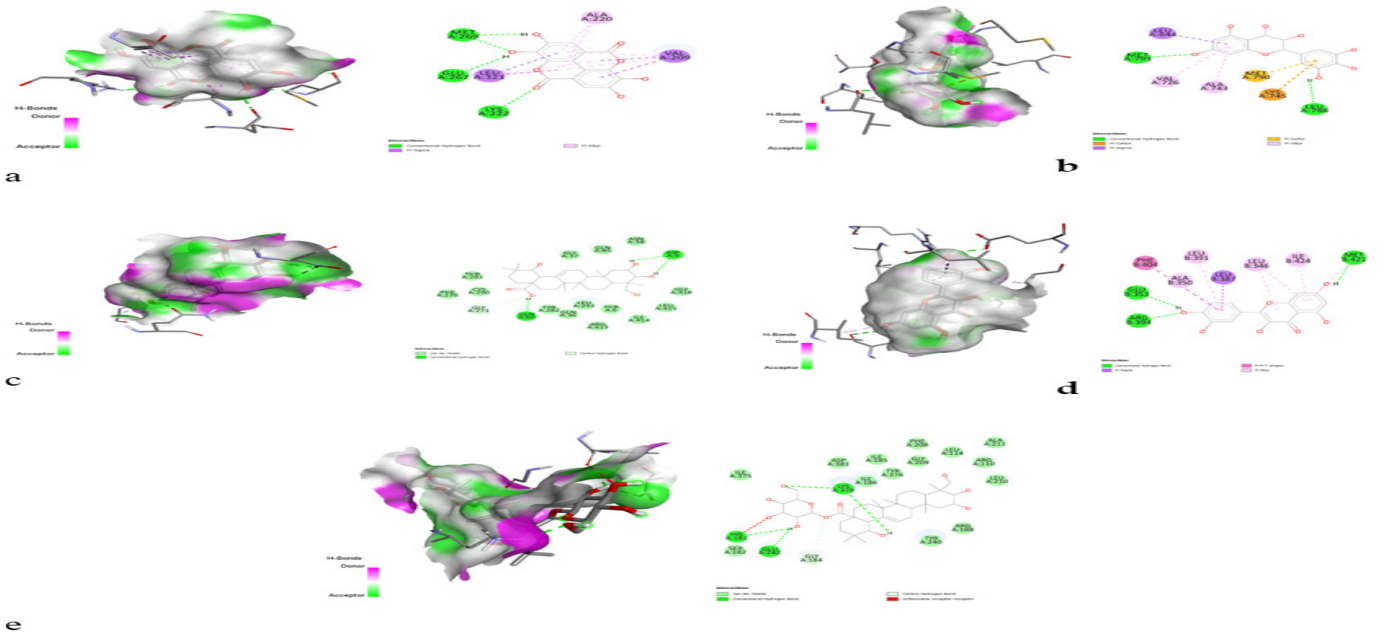

Figure 4: Compound-Target-Pathway network of *Arjuna* against CAD. (Green nodes: Common targets of Arjuna-CAD, Purple nodes: *Arjuna* bioactive compounds, Blue nodes: Enriched Pathways).

Table 1: Docking result of core phytochemicals and core targets.

Bioactive Compounds	Binding Affinity Kcal/mol-1				
	SRC 3D7T	EGFR 5GNK	ESR1 6VPF	ERBB2 2A91	JUN 3PTG
Ellagic Acid	-9	-8.6	-8.4	-8.6	-8.7
Leucodelphidin	-7.9	-8.8	-7.4	-7.8	-7.4
Arjugenin	-7.8	-7.9	-6.7	-8.8	-8.6
Quercetin	-8.3	-8.7	-8.5	-8.6	-7.9
Arjunglucoside I	-8.9	-8	-7.1	-9	-8.7

or development of atherosclerosis in both men and women (Rokach A *et al.*, 2005). The Rap1 signaling system is complex and multifaceted, influencing various aspects of vascular health and the progression of Coronary Artery Disease (CAD). Rap1 regulates inflammatory responses in the arterial wall, which may accelerate or retard the progression of atherosclerosis (Singh B *et al.*, 2021). Rap1 signaling controls platelet adhesion and activation, which are necessary for haemostasias and thrombus formation. Platelet-derived dysregulation of Rap1 may worsen thrombotic events in CAD (Stefanini L *et al.*, 2015). Insulin Resistance (IR) plays a significant role both in the development and progression of Coronary Artery Disease (CAD) (Nisa U *et al.*, 2015).

When cells do not respond to insulin, a cascade of events which includes endothelial dysfunction, oxidative stress, systemic inflammation, dyslipidemia, and impaired glucose metabolism is triggered which contribute to the formation of atherosclerotic plaques in the coronary arteries leading to increase the risk of heart disease (Yang T *et al.*, 2023).

Adherens junctions are cell-cell connections that are essential for preserving vascular integrity is, its dysregulation is linked to multiple illnesses, including Coronary Artery Disease (CAD) (Gustein DE 2003).

In the context of CAD, an alteration in the adherens junction pathway specifically involving VE-cadherin (vascular endothelial cadherin) can increased vascular permeability, endothelial dysfunction, and plaque instability (Dejana E *et al.*, 2008).

Based on network pharmacology and molecular docking, this study suggests that Arjuna can interact with multiple targets and pathways that are linked to the development and progression of CAD, providing important new information about the potential roles of Arjuna in CAD. The findings of this study are to be considered with its own limitations.

Network pharmacology analysis is often static and doesn't consider the dynamic nature of biological systems and the changing conditions within the body. Network pharmacology analysis produces largely on predictive data, and additional experimental

validation is always necessary to validate the results. Therefore, additional experimental studies to explore these pathways and targets are needed to validate the mechanisms of action.

CONCLUSION

In conclusion, the core compounds of Arjuna-Ellagic Acid, Leucodelphinidin, Arjungenin, Quercetin, and Arjunglucoside I-may modulate Insulin resistance, Adherens junction, and RAP1 signalling pathways by acting on key targets like SRC, EGFR, ESR1, ERBB2, and JUN. Molecular docking studies confirmed these findings, while additional preclinical and clinical research on these compounds is necessary to develop a potential therapeutic entity for the treatment of coronary artery disease.

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ABBREVIATIONS

CAD: Coronary artery disease; **IMMPAT:** Indian Medicinal Plants Phytochemistry and Therapeutics; **PPI:** Protein-Protein Interaction; **ADME:** Absorption Distribution Metabolism Excretion.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study explores the cardioprotective potential of *Terminalia arjuna* in Coronary Artery Disease (CAD) using network pharmacology and molecular docking approaches. Five major phytochemicals-Ellagic acid, Leucodelphinidin, Arjungenin, Quercetin, and Arjunglucoside I-were identified as key bioactive compounds acting on target proteins such as SRC, EGFR, ESR1, ERBB2, and JUN. These compounds were shown to influence pathways related to insulin resistance, adherens junctions, and RAP1 signaling. Molecular docking confirmed strong interactions with these targets. The findings suggest that T. arjuna acts through a multi-target mechanism, supporting its traditional use and warranting further experimental validation.

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