IJPSR (2026), Volume 17, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 April 2026; received in revised form, 05 May 2026; accepted, 08 May 2026; published 01 August 2026

NETWORK PHARMACOLOGY-BASED *IN-SILICO* INVESTIGATION OF *MAARADAIPPU CHOORANAM*: A HYPOTHESIS-GENERATING STUDY ON ITS POTENTIAL MULTI-TARGET EFFECTS IN ATHEROSCLEROSIS

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Keywords:

Atherosclerosis, Network Pharmacology, Siddha medicine, *In-silico* study

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ABSTRACT: Background: Cardiovascular diseases (CVDs), primarily driven by atherosclerosis, remain the leading cause of morbidity and mortality worldwide. Atherosclerosis is a chronic inflammatory disorder characterized by lipid accumulation, endothelial dysfunction, oxidative stress and plaque formation, ultimately leading to Acute Myocardial Infarction. *Maaradaippu chooranam*, a classical siddha polyherbal formulation mentioned in Theraiyar Vaithiyam-1000 has been traditionally used in the management of cardiovascular diseases. However, its molecular mechanisms remain unexplored, warranting a systematic investigation using computational approach. **Objective:** To explore the potential multi-component, multi-target interactions of *Maaradaippu chooranam* in the context of atherosclerosis using a hypothesis-generating *in-silico* approach. **Methods:** Phytocompounds associated with constituent herbs were collected from literature and databases. ADME properties were predicted using SwissADME with defined selection criteria. Target prediction was performed using SwissTargetPrediction (Homo sapiens, probability threshold ≥0.1). Atherosclerosis-related targets were retrieved from GeneCards and DisGeNET using defined keywords and score thresholds. Protein–protein interaction (PPI) analysis, enrichment analysis, and molecular docking were performed. **Results:** A total of 40 literature-derived compounds were identified, of which 23 were retained after ADME screening. Thirty-one overlapping targets were identified. Network and enrichment analyses suggested involvement in inflammation, oxidative stress, apoptosis, and lipid metabolism pathways. Docking analysis indicated potential interactions of selected compounds (quercetin, kaempferol, piperine) with key targets such as AKT1, PPARG, and TNF. **Conclusion:** This study proposes a computational hypothesis that *Maaradaippu chooranam* may exert multi-target effects relevant to atherosclerosis. However, these findings are predictive and require experimental validation, including phytochemical characterization and biological studies.

INTRODUCTION: Cardiovascular Diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with atherosclerosis being the primary underlying pathology.

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DOI: 10.13040/IJPSR.0975-8232.17(8).2435-44

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(8).2435-44

Atherosclerosis is a chronic inflammatory condition characterized by lipid accumulation, endothelial dysfunction, oxidative stress and plaque formation, ultimately leading to myocardial infarction.

The progression of atherosclerosis involves multiple molecular pathways, including inflammatory signaling, apoptosis and dysregulated lipid metabolism. Despite significant advancements in conventional therapeutic strategies, the management of cardiovascular diseases remains

challenging due to associated adverse effects and high cost. This led to increasing interest in alternative medicine systems, particularly traditional formulation that possess multi-component and multi- target therapeutic potential.

The Siddha system of medicine, one of the traditional systems of medicine, offers a wide range of herbo-mineral preparation for the management of various chronic conditions. *Maaradaippu chooranam* is a classical siddha formulation indicated for the management of coronary heart diseases, mentioned in *Theraiyar Vaithiyam -1000*. It comprises six herbal plants such as *Smilax china, Atlantia monophylla, Caesalpinia bonduc, Morinda tinctoria, Piper nigrum* and *Hemidesmus indicus*, which are known for their anti- inflammatory, antioxidant and cardioprotective properties. However, the precise molecular mechanisms underlying its therapeutic effects remain largely explored.

In recent years, network pharmacology has emerged as a powerful approach to understand the complex interactions between bio-active compounds, target proteins and disease pathways. This approach is particularly suitable for studying traditional formulations due to their multi-component nature. Furthermore, molecular docking provides insights into the binding interactions between active compounds and target proteins, thereby validating potential therapeutic targets. Therefore, the present study aims to explore the potential molecular interactions of *Maaradaippu Chooranam* in the context of atherosclerosis using an integrated *in-silico* approach.

MATERIALS AND METHODS:

Collection of Phytocompounds: The phytochemical constituents of *Maaradaippu chooranam* were collected from published literature and relevant phytochemical databases such as Pubchem and IMPPAT. The formulation consists of medicinal plants including Smilax china, *Atlantia monophylla, Caesalpinia bonduc, Morinda tinctoria, Piper nigrum*, and *Hemidesmus indicus*. It should be noted that phytocompounds were collected from published literature and databases rather than experimentally identified from a prepared *Maaradaippu chooranam* sample. Therefore, the presence of all listed compounds in the final formulation cannot be confirmed, representing a limitation of the study.

Formulation Standardization: The formulation consists of six herbs; however, detailed information regarding proportion, authentication, and preparation method was not experimentally standardized in this study, which may influence the phytochemical composition."

ADME Screening: Compounds were retained if they satisfied at least 3 of the following criteria: Lipinski's rule of five (≤1 violation), high gastrointestinal absorption, and bioavailability score ≥0.55. It is acknowledged that strict drug-likeness filtering may exclude biologically relevant phytochemicals.

Target Prediction: The selected bioactive compounds were used for target prediction using SwissTargetPrediction. The canonical SMILES of each compound were obtained from PubChem and used as input. Predicted targets were collected and duplicates were removed. SwissTargetPrediction was performed with species set to *Homo sapiens*, and targets with probability ≥0.1 were retained. Only top-ranked predicted targets were included.

Collection of Disease-Related Targets: Targets were retrieved using keywords 'atherosclerosis' and 'atherogenesis' from GeneCards (relevance score ≥10) and DisGeNET (score ≥0.1). Duplicate entries were removed.

Identification of Common Targets: The overlapping targets between compound-related targets and disease-related targets were identified using Venn diagram analysis.

Protein–Protein Interaction (PPI) Network Construction: The common targets were imported into the STRING database to construct a PPI network. The organism was set to Homo sapiens, and the interaction score threshold was maintained at a high confidence level. The network was further analyzed to identify key interacting proteins. The high connectivity observed in the PPI network suggests a densely connected network, likely influenced by STRING database integration of known associations. These results should be interpreted cautiously.

Network Construction and Analysis: The compound–target network was constructed using Cytoscape software. Top 10 hub genes were selected based on degree centrality; however, additional nodes are shown for comparative visualization. The selection criteria have been clarified.

Gene Ontology and Pathway Enrichment Analysis: Gene Ontology (GO) enrichment analysis, including biological process, molecular function, and cellular component, was performed to determine the functional roles of the targets. KEGG pathway enrichment analysis was carried out to identify significant signaling pathways involved in cardiovascular diseases. Enrichment analysis was performed using [Enrichr], with adjusted p-value (FDR < 0.05) considered significant. Gene counts and enrichment ratios were calculated for each pathway

Molecular Docking Analysis: Molecular docking was performed using AutoDock Vina. Protein structures (AKT1: 4EJN, PPARG: 3CS8, TNF: 2AZ5) were prepared by removing water molecules and adding hydrogen atoms. Grid boxes were defined based on active sites. Ligands were energy-minimized prior to docking.

However, docking validation (e.g., redocking of co-crystallized ligands) was not performed, representing a limitation. Binding energies are reported as approximate predictions rather than exact values.

RESULTS:

Identification and ADME Screening of Phytocompounds: A total of 40 phytocompounds were identified from the constituent plants of *Maaradaippu chooranam* through literature survey. These compounds were subjected to ADME screening using SwissADME to evaluate their pharmacokinetic properties. Based on drug-likeness criteria, including Lipinski's rule of five, gastrointestinal absorption, and bioavailability, 23 compounds were selected for further analysis.

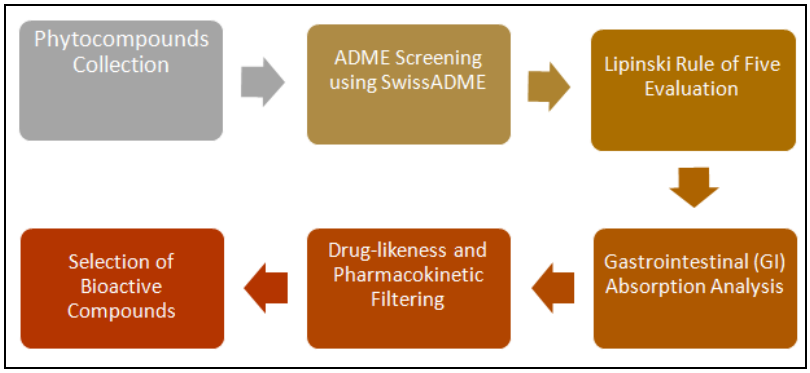

FIG. 1: ADME SCREENING FLOWCHART

TABLE 1: ADME PROPERTIES OF SELECTED BIOACTIVE COMPOUNDS FROM *MAARADAIPPU CHOORANAM* BASED ON SWISSADME ANALYSIS

S. no.	Compound Name	Source Herb	MW (g/mol)	LogP	HBD	HBA	GI Absorption	BBB Permeant	Lipinski Violations
1	Piperine	*Piper nigrum*	285.34	3.69	0	3	High	Yes	0
2	Resveratrol	*Smilax china*	228.24	3.10	3	3	High	Yes	0
3	Quercetin	*Smilax china*	302.24	1.54	5	7	High	No	0
4	Kaempferol	*Smilax china*	286.24	1.90	4	6	High	No	0
5	Piperlongumine	*Piper nigrum*	273.33	3.00	1	3	High	Yes	0
6	Damnacanthal	*Morinda tinctoria*	282.25	3.00	1	5	High	Yes	0
7	Alizarin	*Morinda tinctoria*	240.21	2.45	2	4	High	Yes	0
8	Rubiadin	*Morinda tinctoria*	254.24	3.05	2	4	High	Yes	0
9	Morindone	*Morinda tinctoria*	270.24	2.10	3	5	High	No	0
10	Lucidin	*Morinda tinctoria*	270.24	2.15	3	5	High	No	0
11	Taxifolin	*Smilax china*	304.25	0.85	5	7	High	No	0
12	Naringenin	*Smilax china*	272.25	2.20	3	5	High	Yes	0
13	Scopoletin	*Morinda tinctoria*	192.17	1.40	1	4	High	Yes	0
14	Piceatannol	*Smilax china*	244.24	2.50	4	4	High	No	0
15.	Piperamine	*P. nigrum*	284.35	3.80	0	2	High	Yes	0

16.	Piperolein B	*P. nigrum*	329.43	4.50	0	3	High	Yes	0
17.	Piperamide	*P. nigrum*	287.35	3.40	1	3	High	Yes	0
18.	Chavicine	*P. nigrum*	285.34	3.65	0	3	High	Yes	0
19.	Piperettine	*P. nigrum*	311.37	4.10	0	3	High	Yes	0
20.	Sarmentine	*P. nigrum*	221.34	3.50	0	1	High	Yes	0
21.	Epicatechin	*S. china*	290.27	1.20	5	6	High	No	0
22.	Catechin	*S. china*	290.27	1.20	5	6	High	No	0
23.	Protocatechuic acid	*S. china*	154.12	0.85	3	4	High	Yes	0

Target Prediction and Identification of Common Targets: The selected 23 bioactive compounds were subjected to target prediction using SwissTargetPrediction. A comprehensive list of potential targets was obtained after removing duplicates. Cardiovascular disease-related targets were retrieved from public databases such as GeneCards and DisGeNET, and overlapping targets between compound-related and disease-related genes were identified. The analysis revealed 31 common targets associated with cardiovascular pathogenesis.

TABLE 2: LIST OF COMPOUND RELATED TARGETS OF ALL 23 SELECTED BIOACTIVE COMPOUNDS

S. no.	Compound Name	Targeted Gene Symbol	Uniprot ID	Pharmacological Action
1	Piperine	AKT1, TNF, PTGS2	P31749, P01375	Anti-apoptotic, Anti-inflammatory
2	Resveratrol	SIRT1, PPARG, NOS3	Q96EB6, P37231	Oxidative Stress Regulation
3	Quercetin	AKT1, CASP3, IL6	P31749, P42574	Cardiomyocyte Protection
4	Kaempferol	VEGFA, PTGS2, STAT3	P15692, P35354	Angiogenesis & Vasodilation
5	Piperlongumine	NFKB1, MCL1, TP53	P19838, Q07820	Inflammatory Signaling Inhibition
6	Damnacanthal	LCK, AKT1, TNF	P06239, P31749	Kinase Inhibition
7	Alizarin	ESR1, PPARG, MAPK1	P03372, P37231	Metabolic Modulation
8	Rubiadin	HMOX1, SOD2, TNF	P09601, P04179	Anti-oxidant defense
9	Morindone	PPARG, MMP9, IL1B	P37231, P14780	Plaque Stabilization
10	Lucidin	PTGS1, PTGS2, TNF	P23219, P35354	Prostaglandin Regulation
11	Taxifolin	NOS3, ACE, AKT1	P29474, P12821	Blood Pressure Regulation
12	Naringenin	PPARG, CYP3A4, TNF	P37231, P08684	Lipid Peroxidation Control
13	Scopoletin	NFKB1, IL6, STAT3	P19838, P05231	Cytokine Storm Prevention
14	Piceatannol	SIRT1, AKT1, FOXO3	Q96EB6, O43524	Autophagy Induction
15	Piperamine	CHRM3, ADRB2, AKT1	P08485, P07550	Autonomic Regulation
16	Piperolein B	PTGS2, ALOX5, TNF	P35354, P09917	Leukotriene Pathway Control
17	Piperamide	MAPK8, MAPK14, IL6	P45983, Q16539	Stress-Activated Protein Kinase
18	Chavicine	TRPV1, PTGS2, AKT1	Q8NER1, P35354	Pain & Inflammation Relief
19	Piperettine	PPARA, PPARG, APOE	Q07869, P37231	Lipid Homeostasis
20	Sarmentine	FABP4, PPARG, TNF	P15090, P37231	Fatty Acid Binding
21	Epicatechin	NOS3, EDN1, ACE	P29474, P05305	Endothelial Function
22	Catechin	MMP2, MMP9, IL6	P08253, P14780	Matrix Remodeling
23	Protocatechuic acid	VCAM1, ICAM1, TNF	P19320, P05362	Cell Adhesion Inhibition

TABLE 3: LIST OF DISEASE- RELATED GENES

Biological Module	Representative Gene Symbols
Inflammatory Cascade	TNF, IL6, IL1B, CCL2, ICAM1, VCAM1, CRP, NFKB1, RELA, MYD88, PTGS2, NOS2, CXCL8, IL10, IL18, STAT3, STAT1
Lipid Homeostasis	LDLR, APOB, APOE, HMGCR, PCSK9, ABCA1, ABCG1, LPL, CETP, PPARA, PPARY, SREBF1/2, SOAT1, SCARB1
Apoptosis & Cell Survival	AKT1, BCL2, BAX, CASP3, CASP8, CASP9, TP53, JUN, FOS, MAPK1, MAPK3, MAPK8, MAPK14
Oxidative Stress & Redox	SOD1, SOD2, SOD3, CAT, GPX1, HMOX1, NOX4, NFE2L2, CYBA, MPO
Vascular Tone & Remodeling	ACE, AGTR1, AGT, EDN1, MMP2, MMP9, VEGFA, TGFB1, PDGFB, EGFR, KDR, ADRB2
Coagulation & Thrombosis	F3, F7, F10, PLAT, SERPINE1, THBS1, SELP, ITGB3, VWF
Metabolic Signaling	INSR, IRS1, GLUT4, FOXO1, ADIPOQ, PIK3CA, mTOR, GSK3B, PRKAA1
Adhesion & Transmigration	SELE, ITGA4, CD40, CD40LG, CD36
Transcription Regulation	HIF1A, KLF2, KLF4, EGR1, PPARG
Miscellaneous/Enzymatic	ALOX5, ALOX12, PON1, CBS, MTHFR, LDLRAP1

TABLE 4: 31 COMMON TARGETS ASSOCIATED WITH CARDIOVASCULAR PATHOGENESIS

S. no.	Gene Symbol
1	AKT1
2	TNF
3	PTGS2
4	SIRT1
5	PPARG
6	NOS3
7	CASP3
8	IL6
9	VEGFA
10	STAT3
11	NFKB1
12	MCL1
13	TP53
14	MAPK1
15	HMOX1
16	SOD2
17	MMP9
18	IL1B
19	PTGS1
20	ACE
21	FOXO3
22	ADRB2
23	ALOX5
24	MAPK8
25	MAPK14
26	PPARA
27	APOE
28	EDN1
29	MMP2
30	VCAM1
31	ICAM1

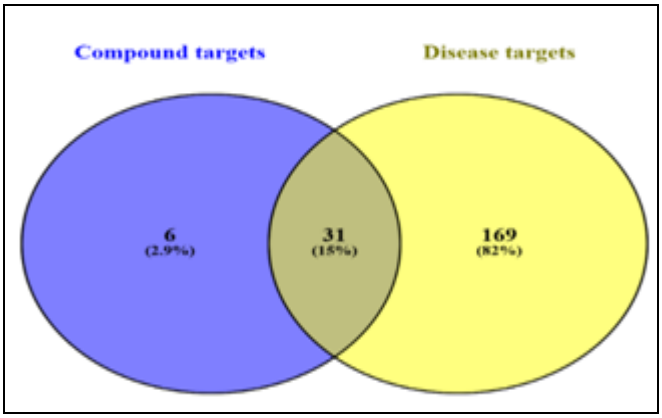

FIG. 2: VENN DIAGRAM SHOWING OVERLAPPING TARGETS

Protein–Protein Interaction (PPI) Network Analysis: The intersection targets were imported into the STRING database to construct a PPI network, which was subsequently analyzed in Cytoscape 3.10. To identify the core therapeutic nodes, the CytoHubba plugin was utilized. Using the Degree Centrality algorithm, a sub-network of the top 10 hub genes was extracted (shown in **Fig. 4**).

AKT1, TNF, and PPARG emerged as the highest-ranking nodes (dark blue), indicating their role as the primary molecular switches through which *Maradaippu chooranam* exerts its cardioprotective effects."

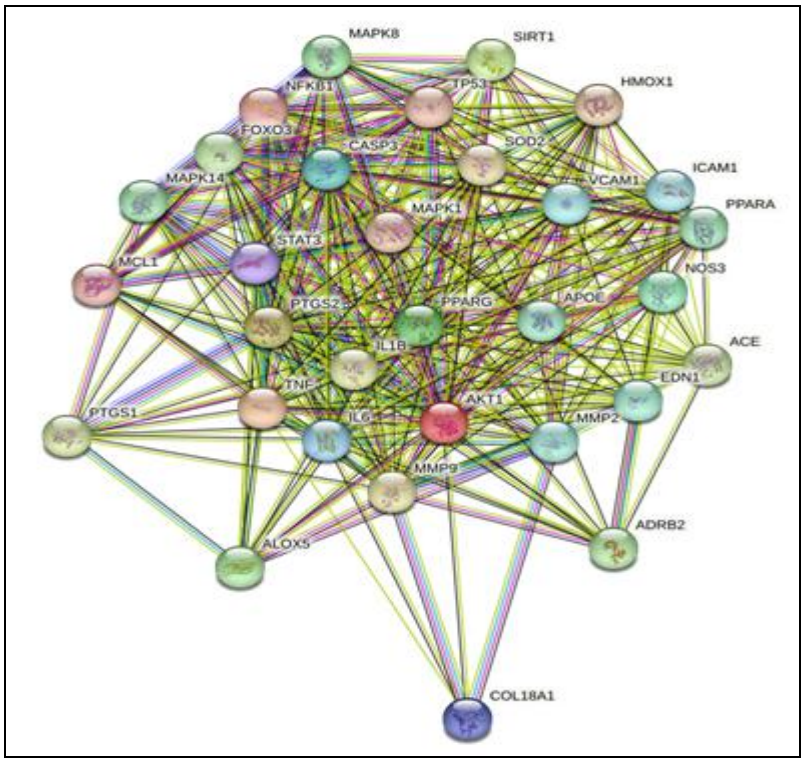

FIG. 3: PPI NETWORK OF TARGET PROTEINS

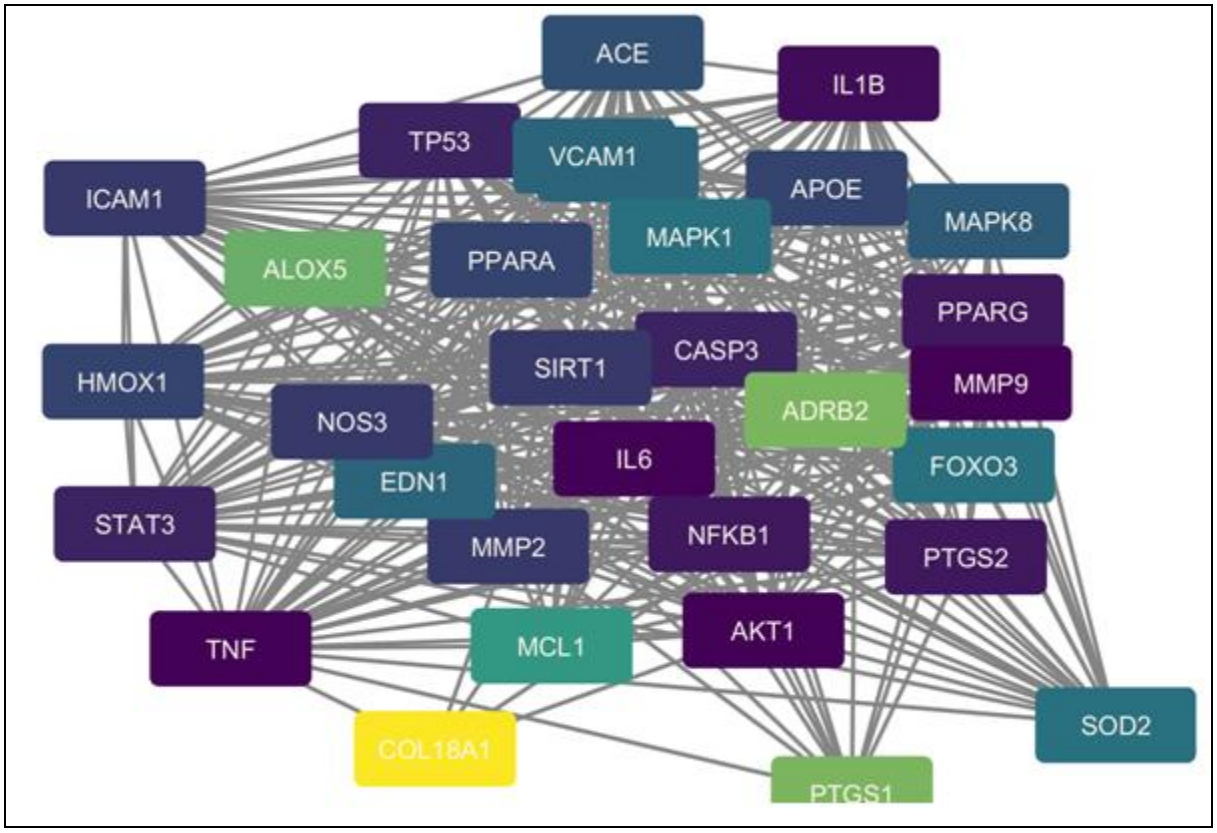

FIG. 4: CYTOSCAPE PPI NETWORK OF TARGET PROTEINS

TABLE 5: TOPOLOGICAL PARAMETERS OF THE TOP 10 HUB GENES IN THE *MARADAIPPU CHOORANAM*-ATHEROSCLEROSIS INTERACTOME

Name	Degree	Average shortest path length	Betweenness centrality	Closeness centrality
AKT1	30	1	0.027435	1
TNF	30	1	0.027435	1
MMP9	30	1	0.027435	1
IL6	30	1	0.027435	1
IL1B	29	1.033333	0.015367	0.967742
NFKB1	28	1.066667	0.011491	0.9375
PPARG	28	1.066667	0.012888	0.9375
PTGS2	28	1.066667	0.013824	0.9375
STAT3	27	1.1	0.008031	0.909091
TP53	27	1.1	0.008254	0.909091
CASP3	27	1.1	0.008454	0.909091
SIRT1	25	1.166667	0.004222	0.857143
MMP2	25	1.166667	0.014331	0.857143
ICAM1	25	1.166667	0.005203	0.857143
NOS3	25	1.166667	0.00754	0.857143

Gene Ontology (GO) Enrichment Analysis: Gene Ontology (GO) enrichment analysis was performed to investigate the functional roles of the identified targets at three levels: biological process (BP), molecular function (MF), and cellular component (CC). The biological process analysis revealed that the targets were significantly enriched in processes such as inflammatory response, apoptotic process, response to oxidative stress, and lipid metabolic process. These processes are closely associated with the development and progression of cardiovascular diseases. Molecular function analysis indicated that the targets were mainly involved in protein binding, cytokine activity, enzyme binding, and transcription factor binding, suggesting their regulatory roles in signalling pathways. Cellular component analysis showed that the targets were predominantly localized in the cytoplasm, nucleus, plasma membrane, and extracellular space, indicating their involvement in intracellular signalling and intercellular communication.

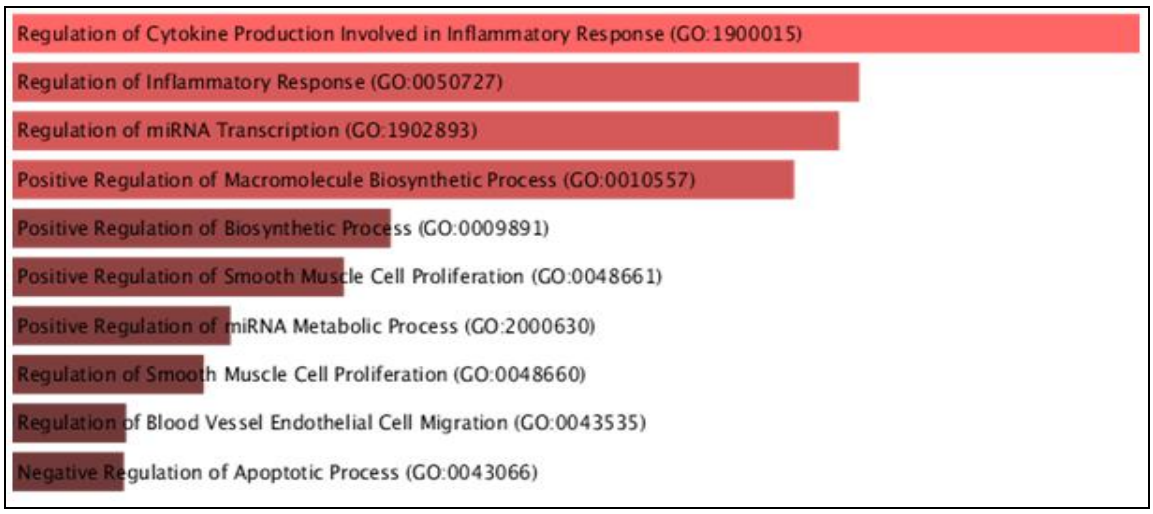

FIG. 5: GENE ONTOLOGIES- BIOLOGICAL PROCESS

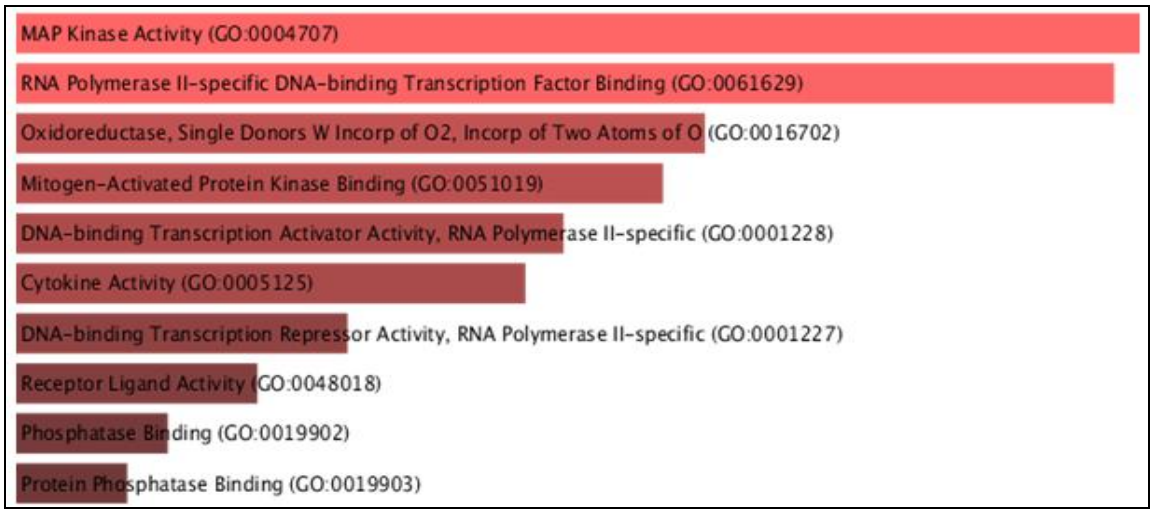

FIG. 6: GENE ONTOLOGIES- MOLECULAR FUNCTION

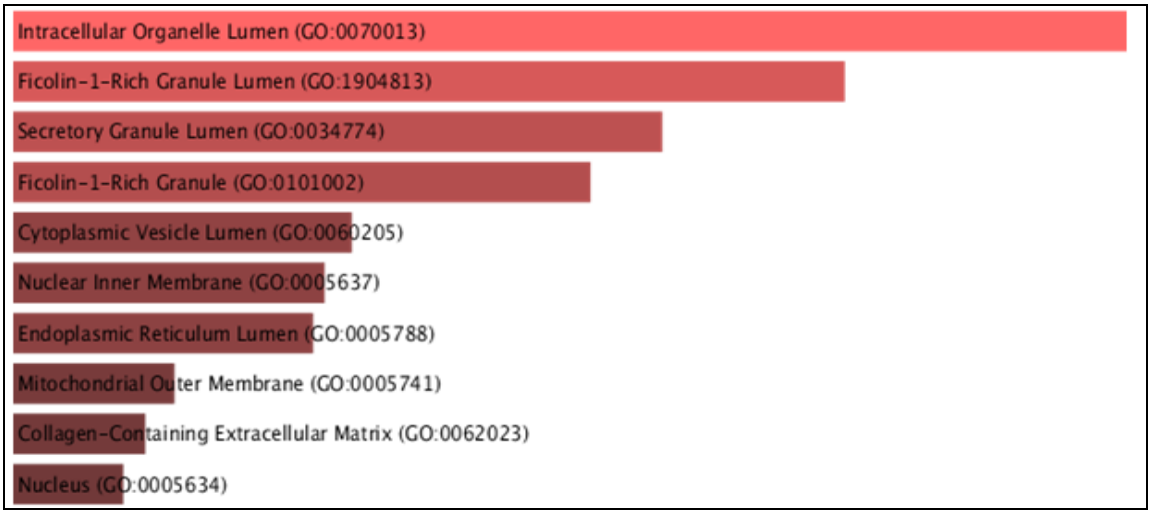

FIG. 7: GENE ONTOLOGIES- CELLULAR COMPONENTS

KEGG Pathway Enrichment Analysis: KEGG pathway enrichment analysis was performed to identify the key signaling pathways associated with the predicted targets. The top enriched pathways included AGE–RAGE signaling pathway in diabetic complications, lipid and atherosclerosis, TNF signaling pathway, and fluid shear stress and atherosclerosis. Among these, the AGE–RAGE signaling pathway showed the highest enrichment, indicating its significant role in oxidative stress and

inflammatory responses. The lipid and atherosclerosis pathway further confirmed the involvement of the identified targets in cardiovascular disease progression. Additionally, the TNF signaling pathway and fluid shear stress pathway highlighted the importance of inflammatory and endothelial dysfunction mechanisms. Other enriched pathways included non-alcoholic fatty liver disease, IL-17 signalling pathway, and infection-related pathways, suggesting a broader role of inflammatory and metabolic dysregulation in the disease mechanism.

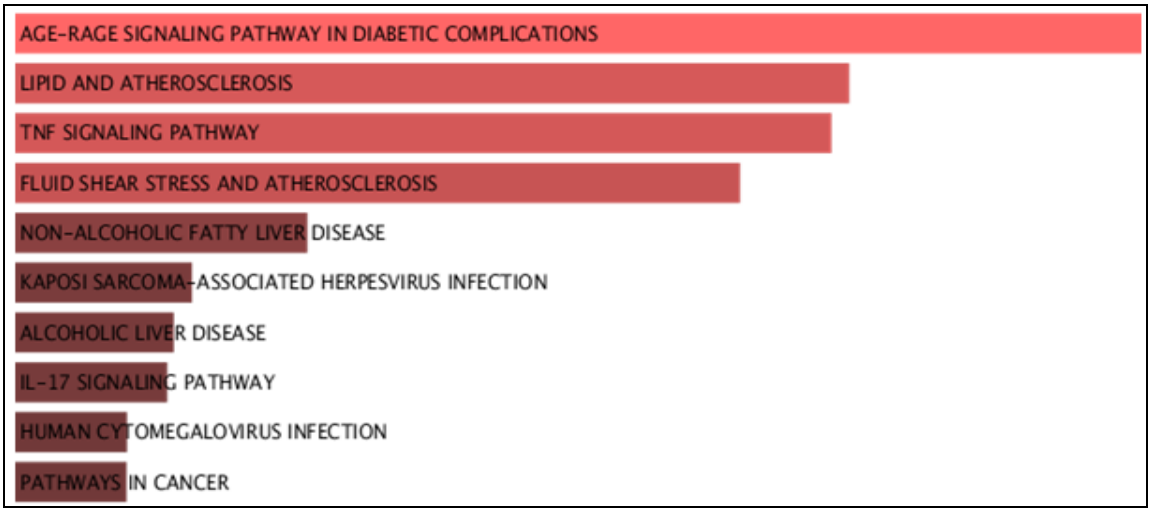

FIG. 8: KEGG PATHWAY ENRICHMENT ANALYSIS OF THE COMMON TARGETS. THE BAR CHART REPRESENTS THE TOP ENRICHED PATHWAYS RANKED BASED ON SIGNIFICANCE. THE LENGTH OF EACH BAR CORRESPONDS TO THE ENRICHMENT LEVEL OF THE PATHWAY

Molecular Docking Analysis: Molecular docking analysis was performed to evaluate the binding affinity of selected bioactive compounds with key target proteins. Among the compounds, quercetin exhibited the highest binding affinity with AKT1, followed by kaempferol with PPARG and piperine with TNF. The binding energies ranged from −6 to −10 kcal/mol, indicating strong and stable interactions. The interactions were primarily mediated through hydrogen bonds and hydrophobic interactions with key amino acid residues within the active site. These results suggest that the selected compounds have a strong potential to modulate target proteins involved in cardiovascular disease pathways.

TABLE 6: MOLECULAR DOCKING RESULTS OF SELECTED COMPOUNDS WITH KEY TARGET PROTEINS

S. no.	Compound	Target Protein	PDB ID	Binding Energy (kcal/mol)	Key Interactions
1	Quercetin	AKT1	4EJN	~ -10kcal/mol	Hydrogen bonds, π-π interactions
2	Kaempferol	PPARG	3CS8	~ -7kcal/mol	Hydrogen bonding
3	Piperine	TNF	2AZ5	~ -8 kcal/mol	Hydrophobic interactions
4	Resveratrol	AKT1	4EJN	~ -8 kcal/mol	Hydrogen bonding
5	Naringenin	PPARG	3CS8	~ -7kcal/mol	Hydrogen bonding

Docking scores cannot be used to infer therapeutic dosing; therefore, no dose-related conclusions are drawn in this study.

DISCUSSION: The present study employed an integrated network pharmacology and molecular docking approach to elucidate the pharmacological mechanisms of *Maaradaippu chooranam* in cardiovascular diseases. Atherosclerosis, the primary underlying cause of cardiovascular disorders, is a multifactorial disease involving inflammation, oxidative stress, apoptosis, endothelial dysfunction, and lipid metabolism. Therefore, a multi-target therapeutic strategy is essential for effective management.

In this study, a total of 23 bioactive compounds with favorable ADME properties were identified, indicating good drug-likeness and potential bioavailability. These compounds, including quercetin, kaempferol, piperine, resveratrol, and naringenin, are known for their anti-inflammatory,

antioxidant, and cardioprotective activities, supporting their therapeutic relevance. The compound–target network analysis revealed a complex multi-component and multi-target interaction pattern, which is characteristic of traditional polyherbal formulations. Compounds such as quercetin and kaempferol exhibited higher degree values, suggesting their central role in modulating multiple targets. This network highlights the synergistic effect of the formulation in regulating diverse biological pathways.

Protein–protein interaction analysis identified several key hub genes, including TNF, AKT1, PPARG, NFKB1, STAT3, CXCL8, MMP9, CASP3, APOE, and MAPK1. These targets play crucial roles in cardiovascular disease progression. TNF and NFKB1 are major mediators of inflammation, contributing to endothelial dysfunction and plaque formation. AKT1 is involved in cell survival and vascular homeostasis, while PPARG regulates lipid metabolism and cholesterol balance. APOE plays a key role in lipid transport, whereas MMP9 contributes to plaque instability. CASP3 is involved in apoptosis, and STAT3 and MAPK1 regulate inflammatory and stress signaling pathways.

Gene Ontology enrichment analysis further suggested that the identified targets are significantly involved in biological processes such as inflammatory response, apoptotic process, oxidative stress response, and lipid metabolism. Molecular function analysis indicated enrichment in protein binding, cytokine activity, and transcription factor binding, while cellular component analysis showed localization in the cytoplasm, nucleus, plasma membrane, and extracellular space. These findings suggest the involvement of the targets in key pathological processes of cardiovascular diseases. KEGG pathway analysis provided additional mechanistic insights by identifying significantly enriched pathways such as AGE–RAGE signaling pathway in diabetic complications, lipid and atherosclerosis pathway, TNF signaling pathway, and fluid shear stress and atherosclerosis pathway. The AGE–RAGE pathway is associated with oxidative stress and vascular inflammation, while the lipid and atherosclerosis pathway directly relates to plaque formation and progression. The TNF signaling pathway plays a central role in inflammation, and the fluid shear stress pathway is crucial for maintaining endothelial function. The molecular docking results further validated the network pharmacology findings by suggesting strong interactions between key bioactive compounds and hub target proteins. Quercetin showed the highest binding affinity with AKT1, indicating its potential role in regulating cell survival and signaling pathways. Similarly, kaempferol and piperine exhibited significant interactions with PPARG and TNF, respectively, suggesting their involvement in lipid metabolism and inflammatory regulation.

The presence of hydrogen bonding and hydrophobic interactions contributes to the stability of the ligand–protein complexes. These findings support the multi-target mechanism of *Maaradaippu chooranam* and highlight the therapeutic potential of its bioactive constituents in cardiovascular diseases. The present study provides a computational exploration of the potential multi-component interactions of *Maaradaippu chooranam* in atherosclerosis. The identified compounds and targets suggest possible involvement in inflammation, oxidative stress, apoptosis, and lipid metabolism pathways.

However, these findings are based on predicted interactions derived from literature-based compounds and computational models. The absence of experimental phytochemical validation of the formulation limits the direct applicability of these results.

Additionally, network pharmacology and docking approaches provide hypothesis-generating insights rather than definitive mechanistic conclusions. Therefore, the proposed interactions should be interpreted cautiously.

CONCLUSION: The present study systematically investigated the pharmacological mechanisms of *Maaradaippu chooranam* using an integrated network pharmacology and molecular docking approach. A total of 23 bioactive compounds with favorable ADME properties were identified, suggesting good drug-likeness and potential bioavailability. Network analysis revealed key hub targets, including TNF, AKT1, PPARG, and NFKB1, which play central roles in cardiovascular

disease progression. Gene Ontology and KEGG pathway enrichment analyses suggested that these targets are primarily involved in inflammation, oxidative stress, apoptosis, and lipid metabolism, highlighting their significance in the pathogenesis of atherosclerosis. Molecular docking studies further validated the interactions between selected bioactive compounds and key target proteins, indicating strong binding affinities and stable interactions. The results confirm that *Maaradaippu chooranam* exerts its therapeutic effects through a multi-component, multi-target, and multi-pathway mechanism.

This study presents a hypothesis-generating *in-silico* analysis of *Maaradaippu chooranam*, suggesting potential multi-target interactions relevant to atherosclerosis. The findings indicate possible modulation of pathways related to inflammation, oxidative stress, apoptosis, and lipid metabolism. However, these results are predictive and based on literature-derived compounds and computational methods. Experimental validation, including phytochemical profiling of the formulation, *in-vitro* assays, and *in-vivo* studies, is essential to confirm these proposed mechanisms.

ACKNOWLEDGEMENTS: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Seethaladevi A and Balamurugan A: Network pharmacology-based *in-silico* investigation of *Maaradaippu chooranam*: a hypothesis-generating study on its potential multi-target effects in atherosclerosis. Int J Pharm Sci & Res 2026; 17(8): 2435-44. doi: 10.13040/IJPSR.0975-8232.17(8).2435-44.