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Research Article

Anti-Atherosclerotic Potential of *Coriandrum sativum* Linn. via Network Pharmacology and *In Silico* Analysis

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Abstract

Background: Atherosclerosis is a complex vascular disorder characterized by lipid dysregulation, oxidative stress, endothelial dysfunction, and chronic inflammation. *Coriandrum sativum* Linn., known as *Dhanyaka* in Ayurveda, has been traditionally used for its cardioprotective and anti-inflammatory properties. Among its phytoconstituents, caffeic acid has been reported to possess antioxidant and lipid-modulating activities, suggesting possible therapeutic relevance in atherosclerosis. Objectives: To investigate the anti-atherosclerotic potential of phytoconstituents of *Dhanyaka* using a systems biology approach integrating network pharmacology and molecular docking. Methodology: Phytoconstituents of *Dhanyaka* were retrieved from IMPPAT and Dr. Duke's phytochemical databases. Drug-likeness and pharmacokinetic properties were evaluated using SwissADME. Potential protein targets of the identified bioactive were predicted through BindingDB and UniProt. Atherosclerosis-related genes were collected from GeneCards, and overlapping targets were identified. Protein–protein interaction (PPI) analysis was performed using STRING, followed by KEGG pathway enrichment analysis. Network visualisation was conducted using Cytoscape, and molecular docking was performed to evaluate ligand–protein binding interactions. Results: A total of 36 overlapping targets associated with both *Dhanyaka* phytoconstituents and atherosclerosis were identified. Network analysis revealed key targets, including FABP1, FFAR1, and PPARA, involved in lipid metabolism and inflammatory regulation. KEGG enrichment highlighted significant pathways such as PPAR signalling, cholinergic synapse, and nitrogen metabolism. Molecular docking demonstrated strong binding affinity of caffeic acid with FABP1, FFAR1, and PPARA, indicating stable ligand–protein interactions within their active sites. Discussion: The findings suggest that caffeic acid from *Dhanyaka* exerts anti-atherosclerotic effects through multi-target modulation of lipid metabolic pathways, inflammatory mediators, and endothelial regulatory mechanisms. Conclusion: *Dhanyaka* act as a promising multi-target phytotherapeutic candidate for the management of atherosclerosis, warranting further experimental and clinical validation.

Keywords: *Coriandrum sativum* Linn, *Dhanyaka*, Caffeic acid, Atherosclerosis, Network pharmacology, Molecular docking, FABP1, PPARA, FFAR1, Neuroactive ligand-receptor pathway, Cholinergic pathway, PPARA-signalling pathway

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Introduction

Atherosclerosis is a progressive cardiovascular disorder characterized by the thickening and hardening of arterial walls due to the accumulation of atherosclerotic plaque within the intimal layer of arteries. This plaque primarily consists of lipids such as cholesterol, cellular debris, fibrin, and calcium deposits, contributing to luminal narrowing and reduced arterial elasticity. (1) The pathogenesis involves lipid accumulation and chronic inflammation within the vascular endothelium, ultimately increasing the risk of severe clinical complications, including myocardial infarction (MI) and stroke. Atherosclerosis predominantly affects the elderly population and is currently one of the leading causes of morbidity and mortality worldwide. (2)

According to the World Health Organization, cardiovascular diseases, with atherosclerosis as the leading cause of death globally, account for approximately 17.9 million deaths each year. (3) Risk factors for developing atherosclerosis include hypertension, which is associated with atherosclerosis, as hemodynamic shear forces weaken the vessel wall and can induce plaque rupture. Other factors include age, male sex, diabetes, obesity, and precursors of inflammation. Atherosclerosis is a

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chronic vascular disease characterized by lipid accumulation, inflammation, oxidative stress, endothelial dysfunction, and the formation of foam cells. NADPH oxidase-generated reactive oxygen species (ROS) trigger LDL oxidation, endothelial activation, and the expression of adhesion molecules, creating a vicious cycle that underlies plaque development and instability. (4, 5) Managing risk factors for atherosclerosis should involve reducing LDL cholesterol, blood pressure, and blood sugar levels through lifestyle changes, inflammation management, and control of autoimmune disorders. (6) Addressing atherosclerotic cardiovascular disease (ASCVD) is crucial because it encompasses heart attacks and strokes, which, although preventable, remain a major global health issue. Therefore, healthcare providers need to assess risks, implement management strategies, and adopt more intensive treatments to lower LDL cholesterol levels. (7)

Coriandrum sativum Linn. (*Dhanyaka)*, traditionally found in Ayurveda for the action of cardiac disorders (*Hridroga*) and inflammation and edema (*Shotha*), also has bioactive compounds such as Flavonoids, phenolic acids, and phytosterols. (8) These constituents have been shown in experimental studies to attenuate LDL oxidation, reduce malondialdehyde (MDA) levels, and suppress foam cell formation both *in vivo* and *in vitro*. (9, 10)

In silico approaches such as molecular docking, ADME prediction, and Network pharmacology offer rapid, cost-effective, and target-specific screening of potential therapeutic constituents. These methods screen the pipeline by prioritizing lead compounds for subsequent experimental validation. (11) Our study employs an integrative *in silico* methodology to evaluate the anti-atherosclerotic potential of major *Coriandrum sativum* phytoconstituents against key molecular targets implicated in plaque formation and progression. This approach aims to provide mechanistic insights and prioritized leads for future pharmacological research.

Materials and Methods

Identification and Retrieval of Bioactive Compounds from *C sativum* L.

Phytochemicals from the whole plant '*Coriandrum sativum* Linn.' were systematically collected from two established databases, including the IMPPAT (12) database and Dr. Duke's (13) Phytochemical and Ethnobotanical Database. The combined list of phytoconstituents was curated by removing basic compounds, such as steroids, lipids, and sugars, and eliminating any duplicates. The refined set of bioactive compounds was then screened through the PubChem database to extract the detailed molecular information, including their canonical SMILES representations. These SMILES were subsequently analyzed using the SWISS ADME (14) tool to evaluate the drug-likeness profile and oral bioavailability of the phytochemicals.

Identification of the Protein Targets

The data retrieved from the SWISS ADME were filtered based on key pharmacokinetic criteria, including high GI absorption, Lipinski's rule of 5, and oral bioavailability ≥ 0.55. The selected compounds, along with canonical SMILES notations, were queried in the Binding DB database (15) (an experimentally validated ligand-protein interaction repository using a structural similarity threshold of ≥ 0.85). Corresponding disease-associated targets and their standardized gene names were subsequently retrieved from the Uniprot database. (16)

Identification and Collection of Anti-atherosclerosis Targets and Pathways

Therapeutic targets associated with atherosclerosis were identified using the GeneCards (17) database by searching for the keyword 'Atherosclerosis' to pinpoint potential anti-atherosclerosis targets. The overlapping gene targets between *C sativum* L. and atherosclerosis were then identified using the Venny 2.1.0 tool for comparative analysis.

Integrated Pathway and Interaction Network Analysis of Atherosclerosis-associated targets influenced by *C sativum* L Bioactives

The obtained overlapping gene IDs of the targets were assessed in the STRING 11.0 version (17) to identify the top ten molecular KEGG pathways most significantly associated with atherosclerosis disease pathogenesis, with the false discovery rate (FDR) value <= 0.05. (18) To enhance the accuracy of the study, protein-protein interaction (PPI) networks identified through STRING were mapped using the overlapping gene IDs, selecting *Homo sapiens* as the reference organism. These interactions, associated with the disease atherosclerosis, were further subjected to biological pathway with the disease atherosclerosis, were further subjected to biological pathway enrichment analysis using the KEGG database, and subsequently downloaded the obtained data for interpretation.

Construction and Network Topological Analysis of Gene-Compound, Pathway-Target, and Integrated Compound-Target-Pathway Model

Following the integration of target genes, bioactive phytochemicals, and associated pathways, network construction was performed using Cytoscape software version 3.7.2. (19) Three distinct interaction networks were generated and analyzed, such as phytochemical compound-target, pathway-target, and gene-phytochemical compound networks. Topological analysis was carried out using the network analyzer tool within Cytoscape. Key therapeutic targets related to atherosclerosis, along with core phytochemicals from *C sativum* L, were identified based on node degree centrality.

Molecular Docking Assessment of Core *C sativum* Phytochemicals against Atherosclerotic Targets

The 3D crystal structures of the top four compounds and the three principal target proteins were obtained from the PubChem and RCSB PDB Protein Data Bank, (20) respectively. Protein preparation was carried out using BIOVIA Discovery Studio by removing water molecules and adding polar hydrogens. Subsequently, molecular docking was performed using PyRx software (21) to predict the binding affinities between the ligands and target proteins. The interactions showing the highest docking scores were further visualized in both two-dimensional and three-dimensional formats using BIOVIA Discovery Studio.

Results

Identification and Retrieval of Bioactive Compounds from *C sativum* L.

After the compilation and deduplication were removed, which gives a total of 420 phytoconstituents of *C sativum* L. by merging data from the IMPPAT database and Dr. Duke's Phytochemical and Ethnobotanical database, these compounds were subsequently screened in the PubChem database to retrieve their canonical SMILES, which were then analysed using the SwissADME tool. Based on key pharmacokinetic criteria, high gastrointestinal (GI)

absorption, zero violations of Lipinski's rule of five, and an oral bioavailability score ≥ 0.55, a final set of 294 phytochemicals was selected, indicating potential drug-likeness.

Identification of the Protein Targets

The canonical SMILES of individual phytochemicals were submitted to the BindingDB database with a structural similarity threshold of ≥0.85 to identify potential protein targets. This screening yielded protein target data for 30 phytochemicals, resulting in a total of 169 associated protein targets. These protein entries were subsequently analysed through UniProt ID mapping to retrieve their corresponding gene identifiers, specifically filtered for *Homo sapiens.*

Identification and Collection of Anti-atherosclerosis Targets and Pathways

A total of 5,852 atherosclerosis-related protein targets were retrieved from the GeneCards database using the keyword 'Atherosclerosis.' Separately, 57 protein targets associated with *C sativum* L. phytochemicals were identified. These two datasets were compared using the Venny 2.1.0 tool, resulting in 36 overlapping targets common to both the disease and the phytochemicals.

Integrated Pathway and Interaction Network Analysis of Atherosclerosis-associated targets influenced by *C sativum* L. Bioactives

The 36 overlapping targets were imported into the STRING database to construct a protein–protein interaction (PPI) network, selecting *Homo sapiens* as the reference organism to map interactions between compound and disease-related proteins. KEGG pathway enrichment analysis identified 9 significant pathways associated with atherosclerosis.

Construction and Network Topological Analysis of Gene-Compound, Pathway-Target, and Integrated Compound-Target-Pathway Model

These 36 target genes, along with phytochemicals and the 9 enriched pathways, were used to construct a comprehensive network in Cytoscape software (version 3.7.2). The network was refined by removing unconnected nodes, specifically 4 genes, 2 phytochemicals, and 1 pathway, to enhance visualization and interpretability.

Topological analysis using the Network Analyser plugin identified the top five key targets in the 'Pathway–Target' network: FABP5, FABP3, FFAR1, FABP1, and PPARA. The three most enriched pathways were: Neuroactive ligand–receptor interaction, cholinergic synapse, and PPAR signalling pathway. Additionally, the five core phytochemicals with significant network connectivity were Acetylcholine, Caffeic acid, Palmitoleic acid, Oleic acid, and Petroselaidic acid.

Molecular Docking Assessment of Core *C sativum* Phytochemicals against Atherosclerotic Targets

Ligand–receptor interactions demonstrating lower binding energy values are generally indicative of greater thermodynamic stability. A binding affinity of –7.0 to -6.0 kcal mol^{-1} is typically considered to reflect a strong and favourable interaction within molecular docking studies. Following docking, the top-ranking ligand–target complexes, based on the most negative binding energies, were subjected to detailed interaction visualization using BIOVIA Discovery Studio to elucidate their binding conformations and molecular interactions.

Among the 25 energy scores of binding, four top-performing ligand–target complexes, phytochemical ligands docked against each of the four core target proteins; those exhibiting predicted binding affinities –7.0 to -6.0 kcal mol^{-1} were considered to demonstrate strong interactions. Notably, caffeic acid showed high-affinity binding with FABP1, FFAR1, and PPARA.

Figure 1: Venny 2.1.0 tool representing the 36 targets overlapping between the disease and the drug

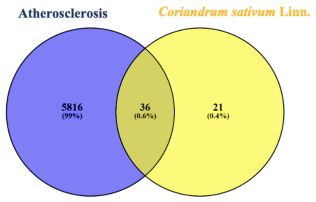

Figure 3: II KEGG Pathway details of the *C stivum* L. protein target interaction pathways on atherosclerosis in *Homo sapiens*

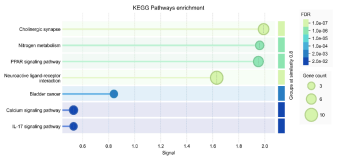

Figure 2: STRING Protein-protein interface for the *C sativum* L. targets on atherosclerosis in *Homo sapiens*

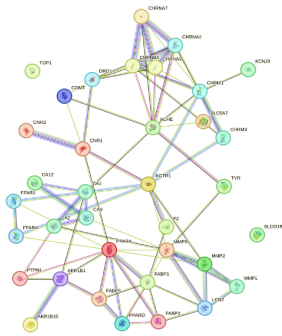

Figure 4: Represents the network interaction between the phytoconstituents of *C sativum* L. with their modulated pathways and protein targets.

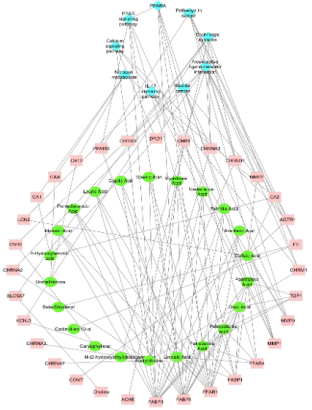

Figure 5: 3D & 2D Docking pose of Caffeic Acid with the target FABP1 (6MP4)

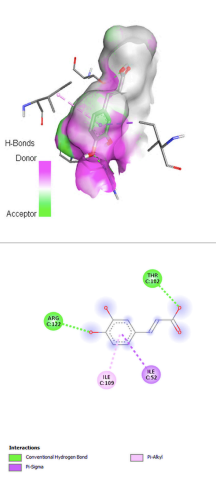

Figure 6: 3D & 2D Docking pose of Caffeic Acid with the target FFAR1 (5TZR)

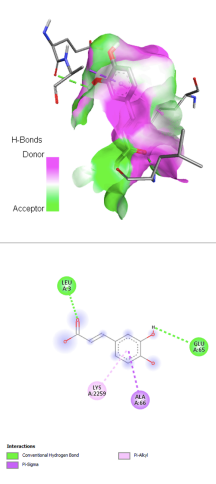

Figure 7: 3D & 2D Docking pose of Caffeic Acid with the target PPARA (3ET1)

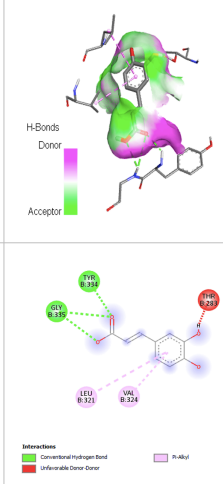

Table 1: Binding affinity between Phytocompounds and Core Target Proteins

Ligand	Receptor (PDB ID)	Energy (kcal·mol $^{-1}$)
Acetylcholine	FABP1 (6MP4)	-4.4
Palmitoleic acid	FABP1 (6MP4)	-6.9
Oleic acid	FABP1 (6MP4)	-5.4
Petroselinic Acid	FABP1 (6MP4)	-4.9
Caffeic Acid	FABP1 (6MP4)	**-7.2**
Acetylcholine	FABP3 (6AQ1)	-3.3
Palmitoleic acid	FABP3 (6AQ1)	-3.7
Oleic acid	FABP3 (6AQ1)	-4
Petroselinic Acid	FABP3 (6AQ1)	-3.9
Caffeic Acid	FABP3 (6AQ1)	-4.7
Acetylcholine	FFAR1 (5TZR)	-4.1
Palmitoleic acid	FFAR1 (5TZR)	-4.8
Oleic acid	FFAR1 (5TZR)	-4.6
Petroselinic Acid	FFAR1 (5TZR)	-4.5
Caffeic Acid	FFAR1 (5TZR)	**-6**
Acetylcholine	PPARA (3ET1)	-4.3
Palmitoleic acid	PPARA (3ET1)	-5.9
Oleic acid	PPARA (3ET1)	-5.1
Petroselinic Acid	PPARA (3ET1)	-5.4
Caffeic Acid	PPARA (3ET1)	**-6.6**
Acetylcholine	FABP5 (7FWI)	-3.6
Palmitoleic acid	FABP5 (7FWI)	-3.8
Oleic acid	FABP5 (7FWI)	-4.2
Petroselinic Acid	FABP5 (7FWI)	-3.6
Caffeic Acid	FABP5 (7FWI)	-5.5

Discussion

Atherosclerosis is considered a chronic and progressive vascular disease marked by lipid accumulation, oxidative stress, endothelial dysfunction, and inflammation within the arterial wall, leading to plaque formation and vascular rigidity. This condition is a major contributor to the global prevalence of cardiovascular diseases, including myocardial infarction and stroke, which remain leading causes of mortality worldwide. Major risk factors include hypertension, diabetes, obesity, aging, and oxidative stress-driven LDL oxidation, all of which promote foam cell formation and plaque instability. Owing to its complex pathogenesis, atherosclerosis necessitates a multi-target therapeutic strategy targeting lipid metabolism, inflammation, and vascular function.

The present study employed an *in silico* systems biology framework to elucidate the anti-atherosclerotic potential of bioactive phytoconstituents from *Coriandrum sativum* Linn. (*Dhanyaka*) through integrated target prediction, protein–protein interaction network analysis, and molecular docking. Among the identified phytoconstituents, caffeic acid demonstrated strong binding interactions with key molecular targets including FABP1, FFAR1, and PPARA, which are critically involved in lipid metabolism and vascular inflammation. These interactions support its potential as a multi-targeted therapeutic agent in the management of atherosclerosis. Caffeic acid is a phenolic compound known for its potent antioxidant and anti-inflammatory properties, which contribute to its atheroprotective effects. It attenuates oxidative stress, a critical driver of endothelial dysfunction, and has been reported in preclinical models to reduce atherosclerotic plaque burden under hyperlipidaemia conditions. Furthermore, caffeic acid favourably modulates lipid metabolism by enhancing HDL levels and exerts immunomodulatory effects through suppression of pro-inflammatory cytokines and signalling pathways associated with vascular inflammation (22–24).

The targets involved in the anti-atherosclerotic activity of *C. sativum* (*Dhanyaka*), including FABP1, FFAR1, and PPARA, play important roles in lipid regulation and inflammatory responses. FABP1 (Fatty Acid Binding Protein 1) contributes to atherosclerosis by regulating intracellular lipid metabolism in macrophages and endothelial cells, and its elevated expression has been associated with plaque formation (26). FFAR1 is involved in metabolic and inflammatory signalling and has been reported to influence macrophage polarization toward anti-inflammatory phenotypes that contribute to tissue repair and resolution of inflammation (27). PPARA (Peroxisome Proliferator-Activated Receptor-alpha) is a nuclear receptor that plays a crucial role in regulating lipid metabolism and inflammation. Activation of PPARA enhances fatty acid β-oxidation and lipoprotein metabolism, thereby limiting lipid accumulation and foam cell formation (28, 29). In addition, PPARA exerts anti-inflammatory effects by down-regulating pro-inflammatory cytokines and promoting plaque stability (30).

The pathway enrichment analysis identified several signalling pathways implicated in atherosclerosis pathogenesis. Among these, neuroactive ligand–receptor interaction pathways are associated with immune modulation and vascular cell signalling. This pathway involves neuropeptides and receptors such as NK1R, which influence vascular smooth muscle cell (VSMC) proliferation and migration, thereby contributing to vascular remodelling and the progression of atherosclerotic plaques (31,32). Additionally, modulation of this pathway has been associated with reduced oxidative stress and enhanced cellular resilience to hypoxic conditions, thereby attenuating vascular injury (33).

The cholinergic synapse pathway, particularly the cholinergic anti-inflammatory axis mediated through α7nAChR receptors, also plays an important role in regulating vascular inflammation. Activation of this pathway suppresses pro-inflammatory cytokines such as TNF-α and IL-6, reduces macrophage activation, and limits plaque development, as demonstrated in ApoE-/- mouse models (34). It further promotes endothelial cell survival and reduces oxidative stress, thereby improving vascular health (35). These mechanisms indicate that modulation of cholinergic signalling may provide vascular protection and slow atherosclerotic progression.

Another key pathway identified in this study is the PPAR signalling pathway, where activation of PPARα plays a central role in maintaining lipid homeostasis and preventing atherogenic changes. PPARα enhances mitochondrial and peroxisomal β-oxidation of fatty acids, reducing intracellular lipid accumulation and foam cell formation within the arterial wall. It also facilitates reverse cholesterol transport by up regulating genes involved in cholesterol efflux to HDL particles and promoting hepatic clearance of lipids, thereby lowering the cholesterol burden in atherosclerotic plaques (36). Furthermore, PPARα improves endothelial function by reducing oxidative stress, enhancing endothelial nitric oxide synthase (eNOS) activity, and increasing nitric oxide (NO) bioavailability, which helps maintain vascular integrity and homeostasis (37). In addition, activation of PPARα suppresses pro-inflammatory cytokines, reduces immune cell

infiltration, and down-regulates endothelial adhesion molecules, thereby stabilizing plaques and slowing disease progression.

The present *in silico* findings have important applications in drug discovery and Ayurvedic pharmacological research. The identification of caffeic acid as a key bioactive compound targeting FABP1, FFAR1, and PPARA provides mechanistic insights into the anti-atherosclerotic potential of *Dhanyaka.* These findings support the traditional cardiovascular applications of Coriandrum sativum and highlight its potential as a multi-target phytotherapeutic candidate for the prevention and management of atherosclerosis. Furthermore, the systems biology approach used in this study may guide future experimental validation, pharmacological studies, and clinical research aimed at developing evidence-based herbal therapeutics. The predicted targets and pathways may also serve as potential biomarkers for evaluating the efficacy of *Dhanyaka*-derived formulations in cardiovascular disorders.

Despite the promising insights, this study is limited by the absence of experimental validation and the static assumptions of molecular docking. Further*, in vitro* and *in vivo* studies are warranted to confirm the therapeutic relevance of phytoconstituents and their identified targets.

Conclusion

Coriandrum sativum Linn. *(Dhanyaka*) was systematically evaluated using *in silico* approaches, including network pharmacology and molecular docking, to explore its therapeutic potential against atherosclerosis. Phytoconstituents identified from curated databases were subjected to ADME screening, followed by target prediction and disease relevance analysis, revealing 36 overlapping gene targets. Subsequent network construction, pathway enrichment, and docking studies highlighted caffeic acid as the most promising compound, exhibiting high binding affinity with key targets are FABP1, FFAR1, and PPARA implicated in lipid metabolism and inflammation. KEGG pathway enrichment further underscored the involvement of pivotal signalling cascades, confirming the mechanistic relevance of *C. sativum* in atherosclerosis. These findings suggest that *Dhanyaka* may be a multi-target phytotherapeutic agent for the management of atherosclerotic disease.

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Conflict of Interest: All authors suggest no conflict of interest

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