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Integration of Network Pharmacology and Molecular Docking to Explore the Multi-Target Mechanism of Green Tea against Coronary Artery Disease

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Abstract: Green Tea (*Camellia sinensis*) is a primordial herb used for centuries to manage coronary artery disease (CAD). However, the mechanism by which green tea-derived chemical components aid in treating CAD is ambiguous. Therefore, in this study, molecular docking and network pharmacology have been unified to reveal the active constituents of green tea and their possible mechanisms against CAD. For this, 5 active reported compounds from green tea, viz., theanine, caffeine, rutin, quercetin, and epigallocatechin, were selected and, using network pharmacology analysis, their interactions with key CAD targets were identified. Out of 102 key targets identified for CAD using network pharmacology and molecular docking, these compounds were found to interact with 48 common genes, including NOS3, NFE2L2, MPO, MMP9, MPP3, MPP2, MCL1, ITGB3, INSR, IL2, HSD11B1, HMOX1, H1F1A, GCK, F2, F10, ESR1, ESR2, EGFR, CYP19A1, CCR5, CA2, BCL2, ALOX5AP, ALOX5, ALOX15, ALDH2, ADRB1, ACE, ABCG2, ABCB1, TP53, STAT1, STAT3, TERT, TNF, SERPINE1, SIRT1, PRKCE, PTGS1, PTGS2, PLA2G2A, PLA2G5, PLG, PLA2G10, PIK3CG, PIK3CA. From these, 5 genes (TERT, MMP2, MPO, CA2, and MMP9) were further studied to explore their potential in CAD based on interaction frequency, binding affinity, and biological relevance to CAD. The identified active constituents of green tea have been shown to effectively prevent and manage CAD through multiple signaling pathways. This study will thus assist in developing herbal formulations or drugs based on green tea extracts, and further in vivo studies for its effectiveness in CAD can be proposed.

Keywords: coronary artery disease; network pharmacology; docking; atherosclerosis; green tea.

1. Introduction

Among the most prevalent cardiovascular disorders impacting people globally is coronary artery disease (CAD), which also tends to be the world's largest cause of mortality, particularly in low- and middle-income nations [1]. Despite the easy accessibility of treatment for its management, more than 7 million deaths and 129 million people have still been found to suffer, putting a huge global economic burden [2]. Constriction of blood vessels reduces blood supply to the heart muscle, leading to myocardial infarction (MI). Therefore, managing CAD will improve anginal symptoms, prevent acute MI, and reduce early mortality [3]. Along with medical therapy, which mainly focuses on controlling angina and preventing plaque

progression, there are certain invasive techniques available that seek to restore sufficient blood flow to affected myocardial regions because of severe coronary stenosis or vascular blockage. These strategies include coronary artery bypass grafting and percutaneous coronary intervention (PCI) [4]. The clinical manifestations of atherosclerotic CAD are diverse and include complications like angina, MI, and cardiac arrest [5]. The findings of coronary angiography demonstrated that environmental factors (obesity, smoking, alcohol consumption, high or low blood pressure, atherogenic diet, etc.) do not contribute to the etiology of CAD in entities with a positive family history [6].

The primary etiopathogenetic process underlying CAD is atherosclerosis, and both genetic and environmental factors can influence the disease's development, either directly or indirectly [7]. Strong chemotactic agents, such as oxidized or modified LDLs, stimulate the production of intercellular and vascular cell adhesion molecules at the endothelial surface, facilitating their adherence and migration into the subendothelial region [8]. The coronary arteries, which cover the whole heart, carry blood to the heart. Accumulation of lipids, smooth muscle proliferation, and endothelial dysfunction leads to constriction in these blood vessels, resulting in chronic heart disorder (CHD) [9]. Controllable risk factors such as obesity, hyperglycemia, hypertension, hypercholesterolemia, smoking, etc., further aid in its progression. Traditional methods of managing these conditions involve consuming nourishing foods, engaging in physical activity (exercise), traditional beverages, and dietary choices [10].

Green tea, obtained mainly from *Camellia sinensis* (family Theaceae), is the most commonly consumed tea in Asia due to its remarkable benefits, including antimicrobial, antioxidant, neuroprotective, anticancer, and anti-obesity effects. It also helps in regulating various cardiovascular complications like MI, stroke, etc., by lowering LDL and cholesterol levels [11,12]. The effects are believed to be due to presence of flavonoids mainly catechins, i.e., (−)-epicatechin (EC, 25- 81 mg/l), (−)-epicatechin-3-gallate (ECG, 16.9-150 mg/l), (−)-epigallocatechin (EGC, 203-471 mg/l), and (−)-epigallocatechin-3-gallate (EGCG, 117-442 mg/l) in green tea [13]. EGCG is, however, the most active and abundant cardioprotective, acting by decreasing inflammatory biomarkers via reduced oxidative stress, reversing endothelial dysfunction, and providing antiplatelet and antiproliferative effects [14,15]. Numerous *in vitro* studies have demonstrated the potential of green tea and its key phytoconstituents, especially epigallocatechin gallate (EGCG), in mitigating key mechanisms of coronary atherosclerosis. EGCG has been shown to inhibit vascular inflammation by downregulating adhesion molecules (VCAM-1, ICAM-1) via suppression of the NF-κB pathway. It also reduces oxidative stress in endothelial cells by lowering ROS levels and activating Nrf2. Furthermore, EGCG inhibits the proliferation and migration of vascular smooth muscle cells, crucial steps in plaque formation, by blocking ERK1/2 and Akt signaling. In macrophage models, EGCG reduces foam cell formation by downregulating scavenger receptors. Additionally, green tea polyphenols promote endothelial repair by enhancing endothelial progenitor cell functions and protecting endothelial cells from apoptosis through PI3K/Akt pathway activation. [15-17]. Several clinical trials have investigated the potential of green tea and its bioactive components in the treatment or prevention of coronary atherosclerosis. Notably, studies have shown that green tea catechins, particularly EGCG, can significantly reduce LDL cholesterol, body fat, and oxidized LDL levels. Trials involving patients with stable angina or carotid atherosclerosis reported improvements in endothelial function and reductions in carotid intima-media thickness. Additionally, long-term observational studies suggest that regular green tea consumption is associated with a lower

incidence of coronary artery disease. These findings collectively support the cardioprotective potential of green tea in atherosclerotic conditions, although larger and longer-term trials are warranted to confirm its clinical efficacy [18-20]. Therefore, the study has been designed to investigate the effects of these chemical constituents on CAD management using network pharmacology, a method that predicts all genomic interactions between selected compounds and their associated ailments, while molecular docking predicts protein-ligand interactions based on binding energy and interaction stimulation [21].

1.1. Pathophysiology of coronary artery disease (CAD).

Atherosclerosis is a chronic inflammatory disease, responsible for the occurrence of various cardiovascular disorders, including CAD, MI, and stroke [22]. It is characterized by thickening or narrowing of arterial blood vessels, mainly due to the deposition of lipid-rich plaques (LDL, cholesterol, fats) in the arteries [23].

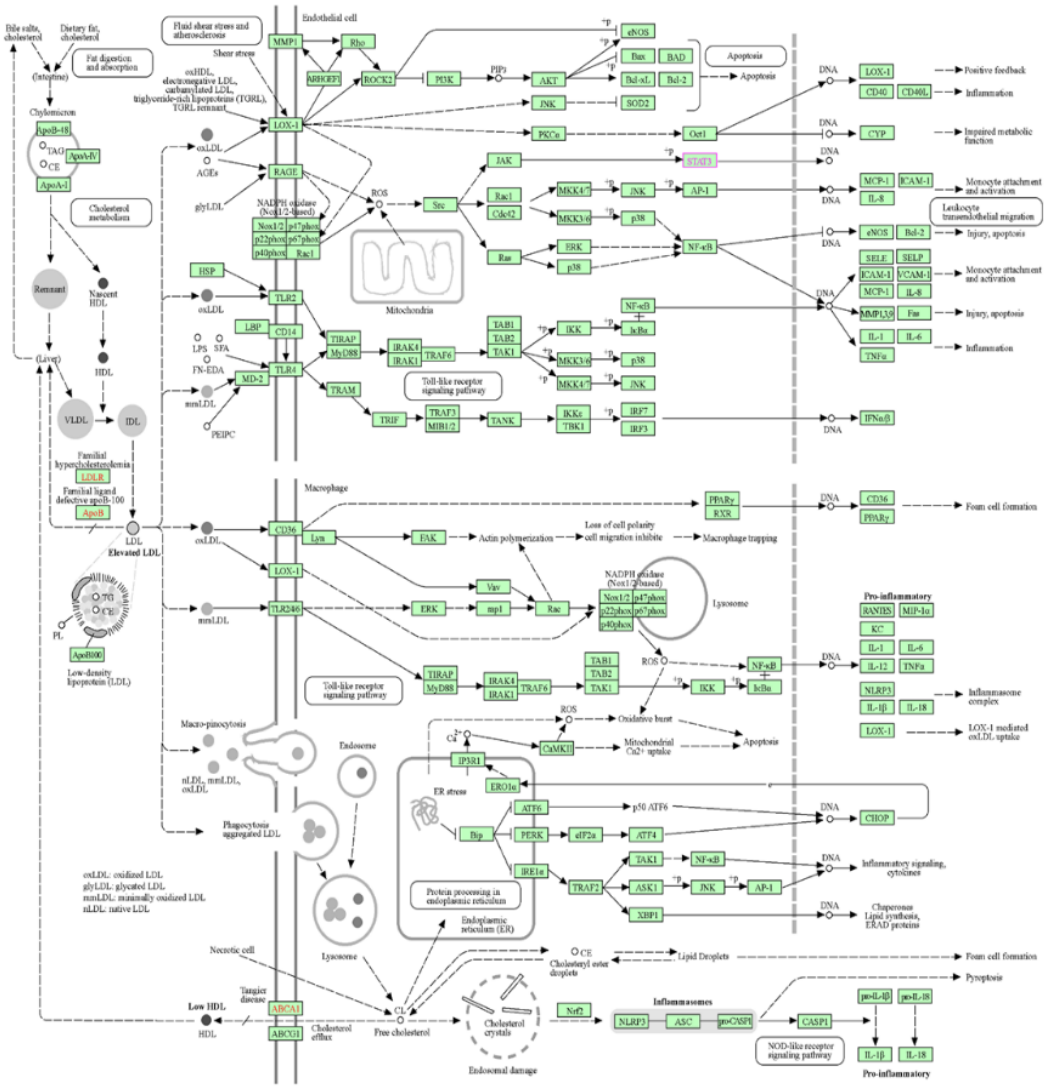


Figure 1. KEGG pathway [This pathway illustrates the various genes associated with the disease such as LOX-1 (responsible for positive feedback and to mediate oxLDL uptake), CD40, CD40L, IL-1, IL-6, and TNF-ALFA (responsible for inflammation), CYP (responsible for impaired metabolic function), MCP-1, ICAM-1, IL-8, VCAM-1 SELE, SELP (responsible for monocyte attachment and activation), eNOS, Bcl-2, MMP-1,3,9, Fas (for initiating the apoptosis of cells), CD36, PPARy (leads to foam cell formation), some proinflammatory complexes including RANTES, KC, MIP-1, TL-1,6,12,1BETA,18, NLRP3 (collectively responsible to initiate the CAD associated problems)].

The high LDL levels primarily constitute a high-risk factor for atherosclerosis. LDL accumulates within arterial vessels and undergoes oxidation, forming oxidized LDL (oxLDL). This oxLDL leads to endothelial dysfunction, resulting in enhanced adhesion and migration of monocytes in the subendothelial space [24]. These monocytes multiply, developing macrophages, which form cholesterol-loaded foam cells by taking up lipoproteins. Eventually, these foam cells die, leaving behind crystalline cholesterol with cell debris [25]. Lectin-like oxidized low-density lipoprotein receptor-1 participates in the identification of oxLDL and is involved in all events underlying the pathogenesis of atherosclerosis (Figure 1) [26].

2. Materials and Methods

The present study includes seven steps: lead identification, PubChem for the canonical smiles, gene identification for selective compounds, DisGeNET for predicting gene-disease association, network pharmacology, and docking to predict all the genomic interactions between the selected compound and ailments, visualization of the network in Cytoscape software, and protein-ligand interactions by molecular docking [27].

2.1. Lead identification.

From the literature, it was found that the health benefits of CAD are mainly attributed to the presence of natural antioxidants, such as polyphenols like caffeine, rutin, theanine, quercetin, and catechins [28]. The concentration of EGCG, EGC, ECG, EC, catechins, and caffeine is found to be 117-442 mg/l, 203-471 mg/l, 16.9-150 mg/l, 25-81 mg/l, 9.03-115 mg/l, and 141–338 mg/l, respectively [13]. Presence of amino acids, *viz*., ascorbic acid, asparagine, glutamic acid, serine, etc., has also been discovered. Out of various chemical constituents present in green tea, five polyphenols, mainly theanine, caffeine, rutin, quercetin, and epigallocatechin-3-gallate (Figure 2), are selected based on their reported data [29].

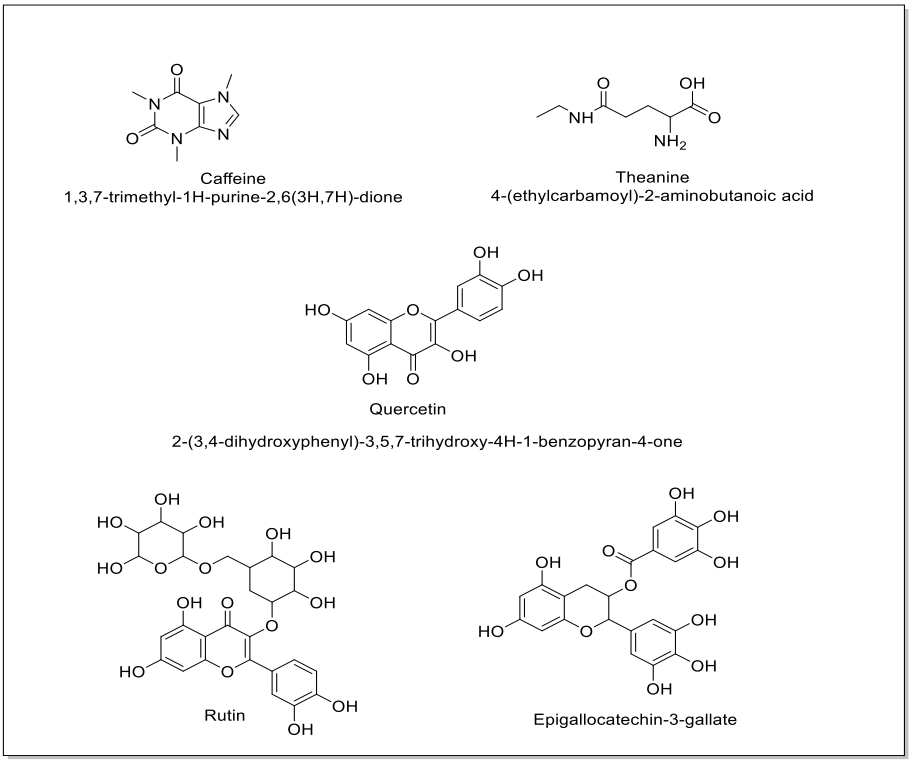


Figure 2. Structures of caffeine, theanine, quercetin, rutin, and epigallocatechin-3-gallate.

2.2. PubChem for the canonical smiles.

Swiss target prediction requires canonical SMILES for identifying key targets associated with the lead compound [30]. These canonical smiles are collected from the reported information in the PubChem and ChemBL databases [31].

2.3. Gene identification for the selective compounds.

Swiss target prediction, an online database, is used for gene identification [32]. Canonical smiles are entered with a species selected as *Homo sapiens*. Using this, the maximum possible macromolecular targets of small bioactive molecules can be estimated [33], as it combines 2D and 3D similarity with a library of approximately 4,00,000 known actives across more than 3000 proteins from three different species.

2.4. Target identification associated with CAD.

The freely available software disgenet is used for target identification when programmed to search for genes associated with CAD [34].

2.5. Target validation.

This approach is used to identify the common linked target between the diseases and lead [35]. Selected steps include creating a node associated with CAD and leading through a string database, studying KEGG pathways, and using advanced MS Excel to optimize the validated target [33].

2.6. Visualization of creation.

The data is collected and visualized as a complex network using Cytoscape software [36].

2.7. Protein and ligand interaction.

Molegro Virtual Docker 6.0 is used to study protein-ligand interactions based on binding energy, moldock score, rerank score, and the number of interactions [37].

3. Results and Discussion

3.1. PubChem for the canonical smiles.

The canonical smiles as generated from the PubChem database for all the selected chemical constituents are CCNC(=O)CCC(C(=O)O)N (theanine), CN1C=NC2=C1C(=O)N(C(=O)N2C)C (caffeine), C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O (Quercetin), C1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O (Rutin), and C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O (epigallocatechin-3-gallate).

3.2. Gene identification for selective compounds.

The genes associated with the constituents, i.e., theanine (102), caffeine (33), quercetin (102), rutin (139), and epigallocatechin-3-gallate (81), as predicted by Swiss target prediction, are illustrated in the Venn diagram, Figure 3.

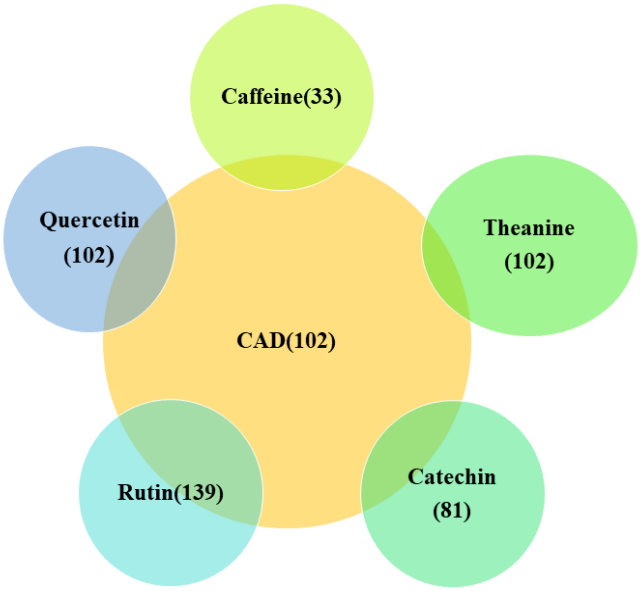


Figure 3. A Venn diagram signifying the number of genes associated with a particular chemical constituent.

3.3. Target identification associated with CAD.

The genes related to disease were identified using Disgenet and linked to 102 targets (Figure 3) previously identified for selected constituents. The KEGG pathway was generated using the string database to study protein-protein interactions [38].

The protein–protein interaction (PPI) network we built for the chosen targets showed a total of 46 nodes (which are proteins) and 350 edges (representing interactions). On average, each protein connects with over 15 others, as indicated by an average node degree of 15.2. The local clustering coefficient averaged at 0.739, hinting that these proteins often group into tightly knit functional clusters. Interestingly, although we would expect only 115 edges by chance in a network of this size, we observed a much higher number of interactions. This led to a PPI enrichment p-value of less than 1.0e-16, which is statistically significant. This suggests that our network isn't just random; it's a highly interconnected and biologically relevant system. The increased density of interactions supports the idea that the selected targets are functionally related and likely play roles in shared or complementary pathways linked to the disease mechanism we're investigating [38].

3.4. Target validation.

Data related to a common-linked target between the disease and the chemical constituent are studied using an advanced MS Excel tool with the VLOOKUP formula.

3.5. Visualization of creation with the effect of different pathways.

A network is created using Cytoscape software, and the data linked is observed. About 48 common genes are associated with CAD and chemical constituents.

ACE (Angiotensin-converting enzyme) is responsible for the conversion of angiotensin I to angiotensin II, leading to the release of terminal His-Leu, which sequentially increases the vasoconstrictor action of angiotensin. In addition, it also causes inactivation of bradykinin, an effective vasodilator. This vasoconstriction will lead to narrowing of the coronary artery, producing symptoms of CAD [39].

SERPINE1 (Serine Protease Inhibitor) or Plasminogen activator inhibitor 1 (PAI-1) inhibits the activity of plasminogen activators (tissue-type, t-PA, and urokinase-type, u-PA) involved in activation of plasminogen into plasmin and thus helps in regulating fibrinolysis and maintaining hemostasis [40]. PAI-1 also helps in cell migration and the breakdown or replacement of body tissues.

STAT1 (Signal transducer and transcription 1-alpha/beta mediator) stimulates interferon (α and β), cytokine (KITLG/SCF), and other growth factors. The interferon binds to receptors and signals protein kinase, leading to Jak kinases (TYK2 and JAK1) activation and STAT1 and STAT2 phosphorylation. These phosphorylated molecules dimerize and combine with ISGF3G/IRF-9 to produce the ISGF3 transcription factor complex, which moves into the nucleus. It is associated with the development of CAD by causing inflammation and endothelial dysfunction [40].

SIRT1 (Sirutin-1), a NAD-dependent protein deacetylase, controls various transcriptional processes and manages numerous cellular activities like cell cycle, metabolism, apoptosis, etc. [41]. SIRT1 acts as a cardioprotective by regulating nitric oxide synthase expression and by impeding ischemia-induced endothelial dysfunction; thus, treatment with SIRT1 activators can be helpful in managing symptoms of CAD [42].

PIK3CA (Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha) phosphorylates Phosphatidylinositol as well as its subforms to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 formation helps recruit pH domain-containing proteins to the membrane (AKT1 and PDPK1), which further initiates a signaling cascade required for cell growth, development, survival, and proliferation.

IL2 (Interleukin-2), a proinflammatory cytokine produced as a result of antigenic activation by T-cells, is vital for its proliferation. It also regulates immune response by stimulating B-cells, monocytes, glioma cells, etc. As inflammation is directly associated with the progression of CAD, the IL-2 polymorphism also increases the risk of developing the disease [43].

GCK Hexokinase-4 phosphorylates various hexoses like D-glucose, D-fructose, etc. to their corresponding phosphates, i.e., hexose 6-phosphate. It is expressed mostly in pancreatic beta cells and the liver, where it is considered a rate-limiting step in glucose uptake. It has been observed that hypomethylation of GCK leads to the occurrence of CAD [44,45].

PLA2G1B phospholipase A2 enhances the hydrolysis of the 2-acyl groups (Calcium-dependent process) in 3-sn-phosphoglycerides, due to which glycerophospholipids and arachidonic acid (the precursors of the phospholipase A2 family) are released. This leads to inflammation, which is directly linked to the risk of CAD [46].

MMP9 (Matrix metalloproteinase-9, 67 kDa), belonging to the peptidase M10A family, participates in the proteolysis of the extracellular matrix and in leukocyte movement. It possesses significant action in bone osteoclastic resorption. It breaks KiSS1 at Gly-|-Leu bond and type IV and type V collagen into large C-terminal and short N-terminal fragments. Various MMPs increase atherosclerotic plaques and are thus involved in CAD progression [47].

EGFR (Epidermal growth factor receptor), the receptor on which various ligands like EGF, epigen/EPGN, epiregulin/EREG, etc. can bind and activate several signaling cascades, leading to the conversion of various extracellular signals into appropriate cellular responses. Ligand binding triggers dimerization and autophosphorylation of the receptor's cytoplasmic residues, which, in turn, initiates complex signaling cascades.

PLG (Plasmin heavy chain A, short form) is a proteolytic factor involved in several processes related to embryonic enlargement, tumor invasion, and inflammation. It acts as a plasminogen activator, and thus regulates plasmin production to manage fibrinolysis, and CAD is linked with disturbances in the fibrinolysis.

MPO (Myeloperoxidase heavy chain), a peroxidase belonging to the family of peroxidases and a part of the defense system of polymorphonuclear leukocytes, possesses antimicrobial activity. It utilizes hydrogen peroxide to oxidize various halogens, generating hypohalous acids such as hypochlorous acid in physiologic conditions, which is mainly responsible for its microbicidal effect. MPO is closely associated with CAD, and its level increases in various cardiovascular disorders like CAD, angina, MI, etc. [48].

PLA2G5 (phospholipase A2), a calcium-dependent isozyme which catalyzes the hydrolysis of 2-acyl groups in 3-sn-phosphoglycerides like L-alpha-1-palmitoyl-2-oleoyl phosphatidylcholine. PLA2 can cause modifications and deposition of circulating lipoproteins in arteries, leading to an increased risk for CAD. It also regulates the metabolism of phospholipids, producing eicosanoids. These eicosanoids are involved in inflammation and thus CAD [49].

PLA2G10, a calcium-dependent secretory phospholipase from Group 10, catalyzes the hydrolysis of phosphoglycerides. It also releases arachidonic acid from cell membrane phospholipids, producing inflammation.

Endothelial NOS 3 (Nitric oxide synthase) caused relaxation of vascular smooth muscles by generating nitric oxide (NO) through a cGMP-mediated signal transduction pathway. NO also facilitates angiogenesis in coronary vessels. Thus, improvement in NOS functioning can help in managing CAD [50].

MMP3 Stromelysin-1 (from peptidase M10A family) present in atherosclerotic plaques also represents a suitable target to reduce the cardiovascular disorders, mainly CAD, as it causes degradation of fibronectin, laminin, and collagen [51].

MMP2-72 kDa type IV collagenase, a significant metalloproteinase associated with various activities like angiogenesis, tissue repair, cardiac remodeling, inflammation, and degradation of atherosclerotic plaque. It also promotes vasoconstriction by acting on several nonmatrix proteins (endothelial 1 and beta-type CGRP) and thus can serve as an important target for CAD management [52].

MCL1, a member of the Bcl-2 family, regulates apoptosis and maintains viability through interaction with various regulators of apoptosis. It also manages proper cardiac function. Its deficiency leads to cardiomyopathy due to disturbed mitochondrial structure and function [53].

INSR (Insulin receptor-α) binds insulin and leads to the phosphorylation of various intracellular substrates and other signaling intermediates, responsible for its diverse actions. For instance, activation of insulin-mediated pathways such as PKB/Akt, Janus kinase, and MAPK ensures proper cardiac development and contractility [54].

MEOX1 Homeobox protein (MOX-1) is a mesodermal transcription factor helpful in somitogenesis. It stimulates NKX3-2 expression in the sclerotome, and CDKN1A and CDKN2A in endothelial cells, and thus controls vascular cell proliferation.

F2 Activated peptide fragment 1 (Thrombin) is a member of the peptidase S1 family and converts fibrinogen to fibrin by cleaving Arg and Lys bonds. It also activates various factors, including V, VII, VIII, and XIII, and thus maintains blood homeostasis in inflammation and wound healing.

F10 Activated factor X (Factor Xa), a vitamin K-dependent glycoprotein which, in the presence of Va and calcium, converts inactive prothrombin to thrombin (active) during blood clotting, and thus helps in regulating hemostasis.

ESR1 (Estrogen receptor 1) and ESR2 (Estrogen receptor β) are nuclear hormone receptors involved in the transcriptional regulation of proteins linked to various cardiovascular functions. Thus, any alteration in its functioning may give rise to cardiovascular risks like CAD and MI [55].

CCR5C-C (Chemokine receptor type 5) and cytokines (CXC, XC, and CC, etc.) are involved in inflammation and repair in certain cardiac diseases, including CAD. It enhances intracellular calcium and prevents plaque development by regulating the functioning of leukocytes, neutrophils, etc. [56].

CA2 (Carbonic anhydrase 2) regulates fluid secretion in the eye, contributing to intracellular pH management in the duodenal layer. CA also constricts vessels, reducing blood flow, and thus its inhibitors will help manage different cardiac ailments like CAD [57].

Bcl-2 Apoptosis regulator suppresses apoptosis in lymphohematopoietic and neural cells by regulating mitochondrial membrane permeability. It also attenuates inflammation by inhibiting NLRP1-inflammasome activation and IL1B release [58].

ALOX5 (Arachidonate 5-lipoxygenase), family MAPEG catalyzes leukotriene biosynthesis, and thus initiates inflammatory processes by causing activation of ALOX5A protein. Thus, its inhibitors, like MK-886, can help inhibit the biosynthesis of leukotrienes.

PRKCE (Protein kinase C epsilon type) is a serine/threonine-protein kinase enzyme that controls multiple cellular processes involved in neuron growth, immune response, and apoptosis, and mediates various signal transducers. It also influences diverse physiological activities of the cardiac system, such as contraction and relaxation [59].

TERT (Telomerase reverse transcriptase) is a ribonucleoprotein enzyme required for telomere elongation and chromosome replication in eukaryotes. It prevents the proliferation of mitochondrial ROS in coronary arterioles in patients with CAD [60].

TNF (Tumor necrosis factor, membrane and superfamily member 14) is a cytokine secreted by macrophages and is responsible for cell proliferation (viability) as well as differentiation via the TRAF2-TRAF3 E3 ligase pathway. They also stimulate the secretion of lymphocytes and IL-1, which causes inflammation, which in turn is responsible for CAD. TNF also disrupts cardiac function by altering myocardial contractility, peripheral resistance, myocyte apoptosis, and NO production. Thus, its inhibitors can be an effective approach to manage CAD [61,62].

PTGS1 and GS2 (Prostaglandin G/H synthase 1 and 2, respectively) are inflammatory biomarkers that act by converting arachidonate to PGH2 and PGE2, respectively. PGH2 is constitutively expressed under various physiological conditions, such as cancer, renal complications, and endothelial injury, whereas PGE2 is cytoprotective and also generates TXA2, which is responsible for platelet aggregation and smooth muscle vasoconstriction. Their

high levels disrupt homeostasis, cause inflammation and thrombosis, and may further potentiate the risk for CAD [63].

The mitochondrial ALDH2 (Aldehyde dehydrogenase) from the aldehyde dehydrogenase family is another significant target site.

ADRB1 (Adrenergic receptor β1), a G-protein coupled receptor, which binds catecholamines, i.e., epinephrine and norepinephrine, and mediates Ras stimulation via G(s)-alpha- and cAMP-mediated signaling. It also regulates sleep behaviors. But its genetic polymorphisms are connected with cardiovascular complications like CAD [64].

CYP19A1 aromatase, a cytochrome P450 mono-oxygenase, causes the conversion of androgens (C19), i.e., androstenedione and testosterone, to estrogens (C18). The polymorphism in CYP19A1 aromatase is directly responsible for CAD [65].

NFE2L2 (Nuclear factor erythroid 2-related factor 2) is a transcription factor with significant activity in oxidative stress. Its stimulation increases cardiac activity and mitochondrial respiration, reduces inflammation and fibrogenesis. Thus, its activation may provide a new approach to protect against cardiac dysfunction, such as CAD [66].

HSD11B1 corticosteroid (11β-hydroxy dehydrogenase isozyme 1) converts cortisol to cortisone (inactive) and restores glucocorticoid production. Thus, its inhibition or deficiency will prevent the progression of heart failure [67].

HIF1A (Hypoxia-inducible factor 1-α) regulates the transcription of around 40 genes, like vascular EGF, erythropoietin, etc., in conditions of hypoxia to adapt to this particular situation. It also regulates cardiac function and vascularization, as well as tumor angiogenesis [68].

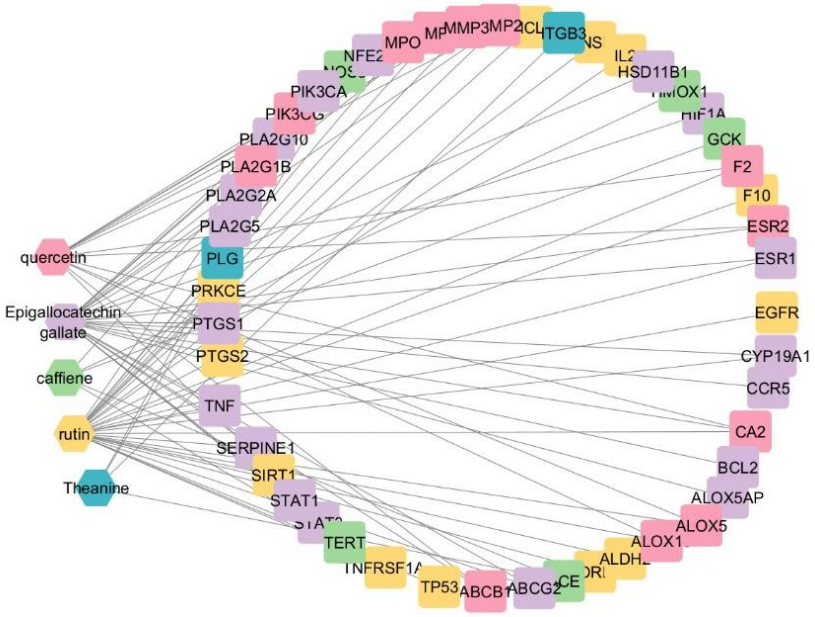


Figure 4. A network of correlation between target genes and selected chemical constituents of green tea.

TP53 (Tumor antigen p53) is a tumor suppressor gene that induces apoptosis under various physiological circumstances, either by up-regulation of BAX/FAS expression or down-regulation of Bcl-2 expression. Its activation may act as a novel target in preventing CAD progression.

ABCB1 and G2 (ABC transport proteins B1 and G2) are ATP-dependent translocases responsible for the translocation of drugs/phospholipids across the membrane. They regulate homeostasis, BP, endothelial function, vascular inflammation, and thrombus formation, and

thus any disturbance in their function may lead to atherosclerotic vascular diseases such as CAD [69].

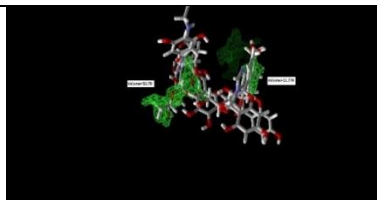
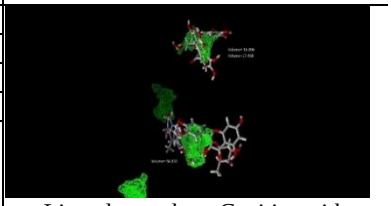
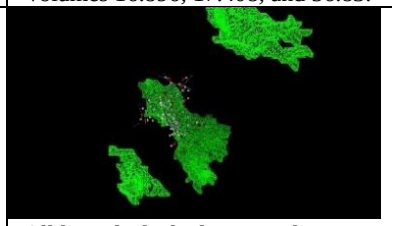
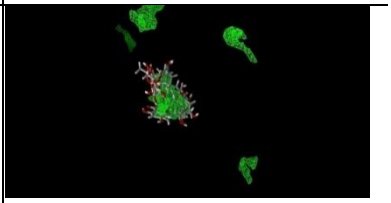
The correlation and visualization of genes with chemical constituents is shown in Figure 4.

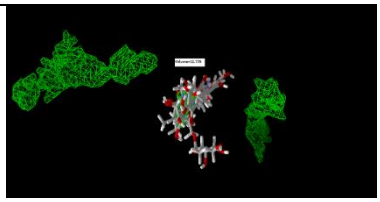
3.6. Protein-ligand interaction.

Based on network pharmacology data, out of 48, five main targets (TERT, MPO, MMP9, MMP2, and CA2) that interact with the majority of chemical constituents have been identified. Considering network pharmacology reports and literature, the PDB IDs for their corresponding genes - TERT (4B18), MMP2 (7XJO), MPO (7LAE), CA2 (5MJN), and MMP9 (1GKC) - have been selected for the molecular interaction study using MVD 6.0 [70,71].

Table 1 shows the moldock score, rerank score, H-bond energy, and interactions for each protein with its selected cavity volume. Most of the active constituents occupy the same cavity volume, such as 7LAE, 5MJN, and 1GKC, whereas 4B18 and 7XJO use two distinct cavity volumes with a good number of interactions. This data (Table 1) shows good binding of selected constituents with their corresponding targets (TERT, MPO, MMP9, MMP2, and CA2).

Table 1. Molecular docking results of selected active constituents with their corresponding PDB ID.

Chemical Constituents	Protein with ID	Mol-Dock score	Re-rank score	H-bond	Interactions	Cavity volume	Docking Views
Theanine	TERT (4B18)	-106.39	-87.03	-6.11	4	33.79	 Ligands use two cavities with volumes of 11.776 and 33.79.
Caffeine		-75.392	-44.66	-4.3	3	11.776	
Quercetin		-109.47	-69.305	-8.286	8	11.776	
Rutin		-168.47	-114.68	-20.066	14	33.79, 11.776	
Epigallocatechin-3-gallate		-139.495	-69.91	-11.435	9	33.79	
Theanine	MMP2 (7XJO)	-90.848	-74.966	-6.89	6	56.83	 Ligands use three Cavities with volumes 16.896, 17.408, and 56.83.
Caffeine		-86.9668	-77.735	-5.5	3	56.83	
Quercetin		-124.54	-86.968	-13.54	11	16.896, 17.408	
Rutin		-162.638	-82.147	-17.45	12	56.83	
Epigallocatechin-3-gallate		-172.734	14.663	-20.449	13	16.896, 17.408	
Theanine	MPO (7LAE)	-78.79	-63.30	-8.6	5	579.0	 All ligands docked in a single cavity with a volume of 579.0.
Caffeine		-64.46	-58.248	-3.58	3		
Quercetin		-115.616	-91.133	-19.166	15		
Rutin		-213.017	-144.92	-19.395	15		
Epigallocatechin-3-gallate		-176.796	-84.648	-19.681	13		
Theanine	CA2 (5MJN)	-89.71	-73.79	-6.5	6	73.216	 All ligands docked in a single cavity with a volume of 73.216.
Caffeine		-70.65	-64.315	-3.4	4		
Quercetin		-114.469	-88.85	-7.328	8		
Rutin		-187.59	-129.19	-16.47	15		
pigallocatechin-3-gallate		-158.419	-110.28	-12.86	12		

Chemical Constituents	Protein with ID	Mol-Dock score	Re-rank score	H-bond	Interactions	Cavity volume	Docking Views
Theanine	MMP9 (1GKC)	-102.24	-83.889	-7.31	4	11.77	 All ligands docked in a single cavity with a volume of 11.77.

4. Conclusions

CAD is associated with deep vein arteriosclerosis, hypertension, and myocardial infarction. A diversity of traditional techniques is available to ameliorate CAD through nourished edibles, exercise, and pharmacological therapy. The study examines the beneficial effects of green tea extracts in CAD using network pharmacology and molecular docking. Five paramount chemical constituents as theanine, caffeine, rutin, quercetin, and epi gallate catechins predict 48 common genes associated with CAD (NOS3, NFE2L2, MPO, MMP9, MMP3, MMP2, MCL1, ITGB3, INSR, IL2, HSD11B1, HMOX1, H1F1A, GCK, F2, F10, ESR1, ESR2, EGFR, CYP19A1, CCR5, CA2, BCL2, ALOX5AP, ALOX5, ALOX15, ALDH2, ADRB1, ACE, ABCG2, ABCB1, TP53, STAT1, STAT3, TERT, TNF, SERPINE1, SIRT1, PRKCE, PTGS1, PTGS2, PLA2G2A, PLA2G5, PLG, PLA2G10, PIK3CG, PIK3CA). Of the total 48 genes, the following 5 genes (TERT, MMP2, MPO, CA2, and MMP9) are commonly targeted by theanine, caffeine, rutin, quercetin, and epigallocatechin. The five prevalent genes TERT (4B18), MMP2 (7XJO), MPO (7LAE), CA2 (5MJN), and MMP9 (1GKC) are specified for molecular docking with selected chemical constituents of green tea, showing good binding of these constituents to the selected PDBs. These five genes were not only frequent and high-affinity targets of the selected phytocompounds but also commonly targeted and highly relevant to CAD progression, distinguishing them from the remaining 43 targets in terms of both computational and biological significance. Literature mining and biological pathway enrichment revealed that these genes play central roles in cardiovascular pathology, including inflammation, endothelial dysfunction, oxidative stress, vascular remodeling, and plaque stability; for example, TERT is linked to endothelial function and aging. MMP2 and MMP9 are key matrix metalloproteinases involved in plaque rupture and tissue remodeling. MPO is associated with oxidative stress and atherogenesis. CA2 regulates pH balance and vascular tone. Therefore, these compounds and genes may be key factors of green tea in treating CAD. Finally, this study may help develop herbal formulations or drugs based on green tea extracts and may further propose *in vivo* studies for CAD.

Author Contributions

Conceptualization, R.S. and S.K.; methodology, A.B.; software, R.S.; validation, J.C., S.K., and A.J.; formal analysis, A.J.; investigation, S.K.; resources, A.B.; data curation, R.S.; writing—original draft preparation, S.K.; writing—review and editing, A.J. and J.C.; visualization, S.K.; supervision, A.J.; project administration, A.B. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors declared no conflict of interest, financial or otherwise.

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