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Research article

Integrated Network Pharmacology and Molecular Docking Analysis of Carvacrol and Paeonol against Hypertension

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Abstract

Hypertension is a severe chronic cardiovascular condition characterized by oxidative stress, inflammation, endothelial dysfunction, and vascular remodeling. Natural phytochemicals have sparked widespread interest due to their multitarget therapeutic potential and attractive pharmacological characteristics. The current study used an integrated network pharmacology and molecular docking technique to evaluate the antihypertensive mechanisms of Carvacrol and Paeonol. SwissTargetPrediction and PubChem were used to identify potential phytochemical targets, while the GeneCards database was searched for hypertension-associated genes. Venn analysis was used to identify common targets, which were then used to create protein-protein interaction networks with STRING and Cytoscape. Gene Ontology and KEGG pathway enrichment analysis demonstrated a substantial role for calcium signaling pathways in hypertension control. Key overlapping targets were ALB, GSK3B, EP300, MAOB, MAOA, ACHE, SLC6A3, CA9, HDAC6, and PRKCA. Molecular docking analysis revealed that Carvacrol and Paeonol have good binding affinities for hypertension-associated target proteins 4N0F and 4J1R. Docking values for Carvacrol were -4.3 and -5.0 kcal/mol, whereas Paeonol had scores of -4.0 and -4.8 kcal/mol. These data indicate that both phytochemicals have prospective antihypertensive properties via multitarget interactions and pathway modification.

1. Introduction

Hypertension is a medical condition characterized by increased blood pressure caused by blood pushing against the walls of the arteries. Long-term high blood pressure can cause cardiovascular disease and nephritis. Systemic arterial hypertension is caused by a variety of variables, including genetics, environment, and inheritance. It is the biggest risk factor for cardiovascular disease, including coronary heart disease, left ventricular hypertrophy, and arrhythmia, the leading cause of mortality worldwide. Hypertension is a significant public health issue, impacting 1.28 billion individuals globally. The frequency of hypertension is rising worldwide, with an anticipated 1.56 billion cases by 2025. Antihypertensive drugs are currently classified into several groups, including beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers. However, their effectiveness to lower the frequency of problems is limited. Certain medications adverse effects might also affect metabolism, and blood pressure must be controlled while simultaneously ensuring the target organ's safety. Despite numerous therapeutic interventions, understanding the complex molecular mechanisms that underpin hypertension and developing effective treatments are ongoing goals. Therefore, creating safer and more diversified antihypertensive medications is critical [1-3].

Investigating the potential of natural compounds using a reverse pharmacology method while considering safety profiles may be a reasonable technique for treating hypertension. In this perspective, medicinal plants continue to be extremely important to humanity since they contribute to the creation of contemporary medications in the healthcare industry [4-8]. Carvacrol, a bioactive chemical found in oregano and thyme, has antioxidant, anti-inflammatory, vasodilator, and cardioprotective properties [9-12]. Similarly, Paeonol, obtained mostly from Paeonia suffruticosa, has potent antioxidant, anti-inflammatory, endothelial protection, and vascular regulation capabilities. Previous study has demonstrated that these phytochemicals impact signaling pathways associated to oxidative stress, inflammation, apoptosis, and vascular dysfunction, which are all crucial to the development of hypertension [13-15].
Network Pharmacology have enabled a thorough knowledge of the multitarget interactions between phytochemicals, proteins, genes, and signaling pathways involved in complicated illnesses. Molecular Docking is a useful computational tool for assessing ligand-target binding interactions and estimating molecular affinity for disease-associated proteins [16-21]. The current study aimed to evaluate the molecular processes and antihypertensive potential of Carvacrol and Paeonol utilizing integrated network pharmacology and molecular docking techniques.

2. Materials and Methods

2.1 Chemical Candidates and Compound Related Targets

The literature was used to aid the chemical selection process. The selected bioactive compounds were then searched in the PubChem database to obtain their chemical structures and Smiles notations. Potential target proteins linked with these chemicals, with potential scores higher than zero, were then predicted using the Swiss Target Prediction Database.

2.2 Identification of Hypertension-Related Targets

We searched the GeneCards database for possible targets related with hypertension. This database combines data from several sources to provide complete information on human genes. The selected targets were collated for additional study and classified as hypertension-related targets [22].

2.3 Venn Diagram

A Venn diagram was created to assess the overlap between hypertension-associated targets and possible targets for Carvacrol and Paeonol.

2.4 Protein-Protein Interaction (PPI) Network

The STRING database (https://string-db.org/) collects known and projected protein-protein interactions, including functional and physical correlations. For this study, we utilized STRING [22] to look at the connections between the chemicals in our analysis and the targets associated with hypertension, finding potential therapy targets. To build a reliable protein-protein interaction (PPI) network for these targets, we employed the "Homo sapiens" organism with a confidence level of 0.9. This confidence score is commonly employed because it strikes a good balance between sensitivity and specificity, resulting in a credible criterion for interaction prediction. As a consequence, only proteins with interaction scores of 0.9 or higher were included to the PPI network, increasing the accuracy of our potential target identification.

2.5 Functional Enrichment And Pathway Analysis

To identify key pathways and related Gene Ontology (GO) concepts, all potential therapeutic targets were analyzed using pathway and GO enrichment analyses in the String database [22] (https://string-db.org/). This investigation shed light on the biological processes (BP), molecular functions (MF), and cellular components (CC) connected with the targets. Pathways and GO keywords having a significance level of $p < 0.05$ were chosen for further study.

2.6 Construction of Compound-Target Network

The compound-target interaction network was created by linking the targets associated with each chemical. Cytoscape 3.10.2 (Cytoscape Consortium, San Diego, CA, USA) was used to visualize the network [23]. Nodes in the network represent drugs and their targets, while edges show their interactions.

2.7 Molecular Docking

Molecular docking investigations were carried out in accordance with the previously published protocol described by Ahmad et al. (2024). The three-dimensional structures of target proteins were obtained from the Protein Data Bank, while ligand structures were obtained from PubChem. AutoDock Vina was used to investigate binding affinity and protein-ligand interactions. The docked complexes with the lowest binding energy were chosen and visualized using PyMOL and Discovery Studio, following the previously defined computational process [22-24].

3. Result and Discussion

3.1 Potential Therapeutic Targets of Compounds and Hypertension

Using hypertension as a keyword, data were gathered from the GeneCards database, resulting in 10642 target genes. Among these, 48 targets were found to be shared by the chemicals and hypertension-related genes, indicating prospective therapeutic targets for compounds used to treat hypertension. These overlapping targets are illustrated in a Venn diagram (Figure 1).

3.2 Compound-Target Network

To investigate the signaling pathways and functional functions of the identified target genes, we used Cytoscape

data analysis. This strategy made it easier to create a sophisticated compound-target network, as seen in Figure 2. The network highlights the pharmacological pathways by which the drugs may impact hypertension therapy, with a focus on interactions with 54 target proteins. Network analysis shows that different components are converging across numerous targets, implying that these bioactive chemicals may have synergistic effects. These interactions may improve the treatment effectiveness of these medications not just for hypertension but also for other associated disorders.

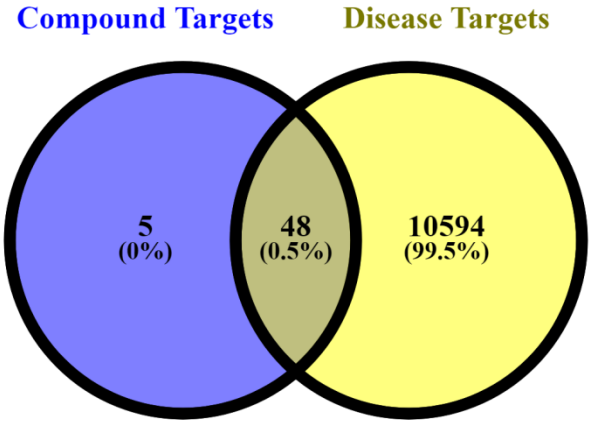


Figure 1. Venn diagram.

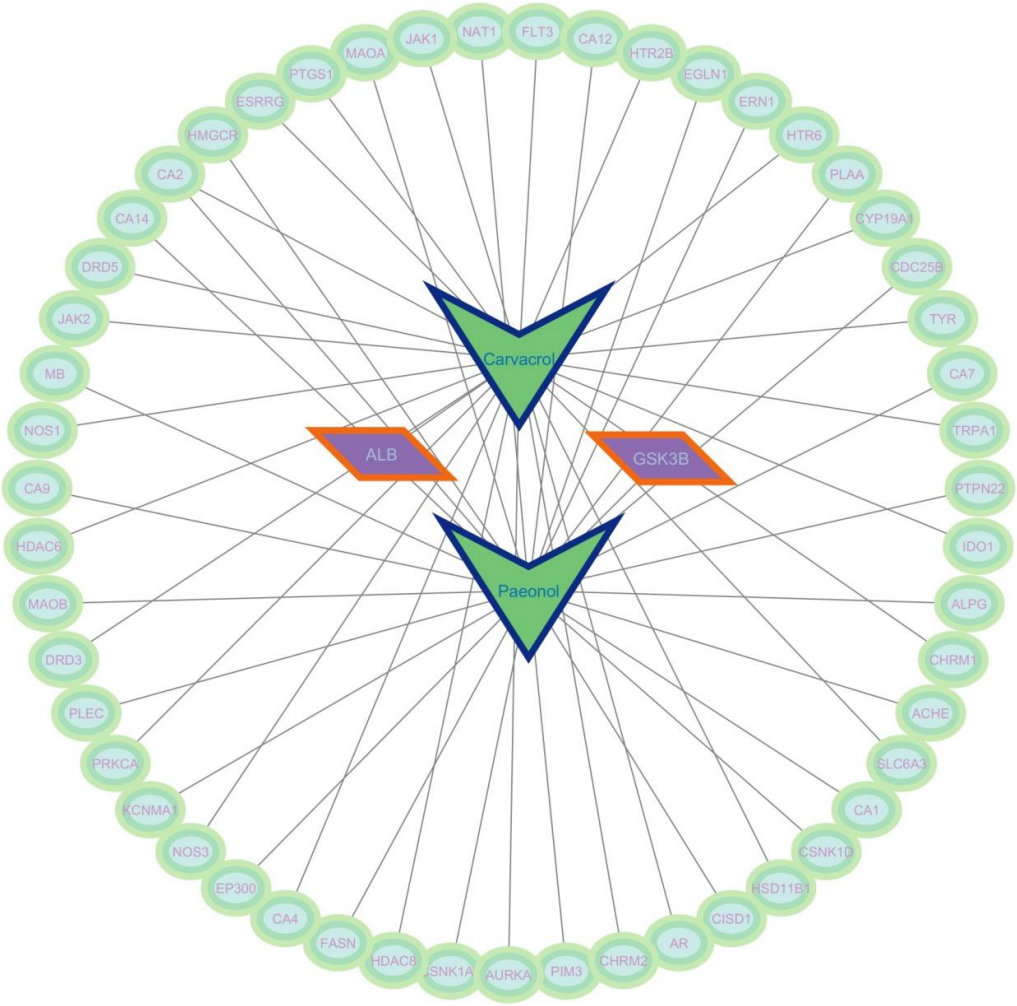


Figure 2. Compound Target Network.

3.3 PPI Network Visualization and Analysis

The STRING database was used to investigate interactions between 48 putative medicinal targets. The final protein-protein interaction (PPI) network included 48 nodes and 128 edges, with an average node degree of 5.33 and a local clustering coefficient of 0.595 (Figure 3). In this network, nodes represent individual proteins, while edges represent the relationships between them. A higher degree value indicates a more important involvement for the protein in the network. Following a filtering procedure using the defined criteria, numerous hub genes were found, including ALB, GSK3B, EP300, MAOB, MAOA, ACHE, SLC6A3, CA9, HDAC6, and PRKCA. These proteins play critical roles in a variety of regulatory processes such as signal transduction and protein phosphorylation. The top five nodal targets were identified as ALB, GSK3B, MAOB, MAOA, and ACHE. The substantial connections between these genes and other possible therapeutic targets highlight their relevance in hypertension management.

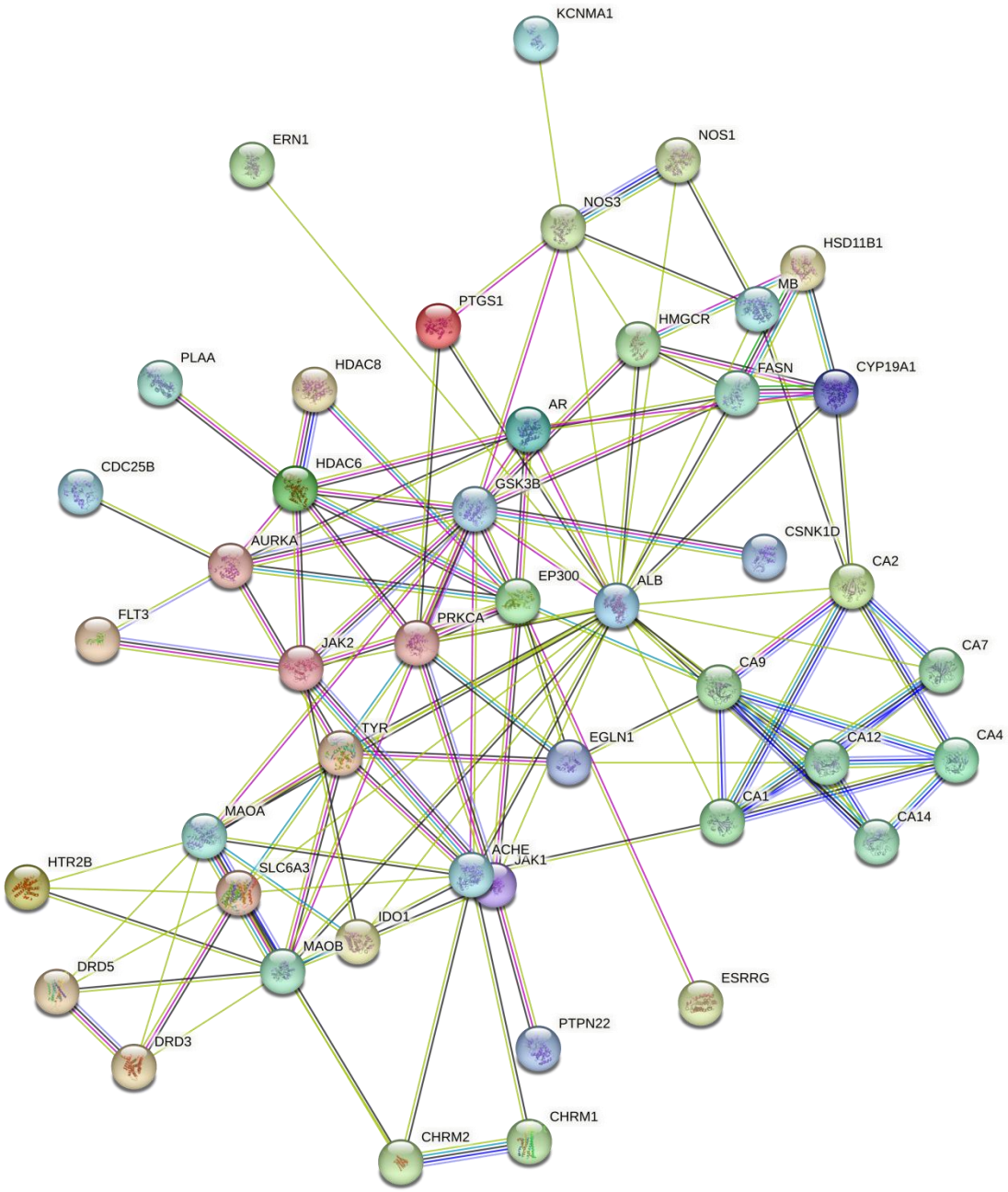


Figure 3. Protein Protein Interaction Network.

3.4 GO Analyses

To elucidate the biological mechanisms through which compounds exert their effects on hypertesion, we conducted Gene Ontology (GO) enrichment analysis on 48 potential therapeutic targets associated with these compounds via the string database. This analysis encompassed three distinct categories: biological process (BP), molecular function (MF), and cellular component (CC). The top ten GO terms identified in each category are presented in a bar plot, with the results detailed in Table 1 (BP), Table 2 (MF), and Table 3 (CC), alongside (Figure 4A), (Figure 4B), and (Figure 4C). In the visualizations, the size of each bar corresponds to the number of enriched genes associated with that GO term, whereas the colour gradient reflects the significance of the p value, with darker shades indicating lower p values. A larger bar denotes a greater number of enriched therapeutic genes within the corresponding GO term, suggesting a stronger association of that term with hypertension treatment than with the other terms.

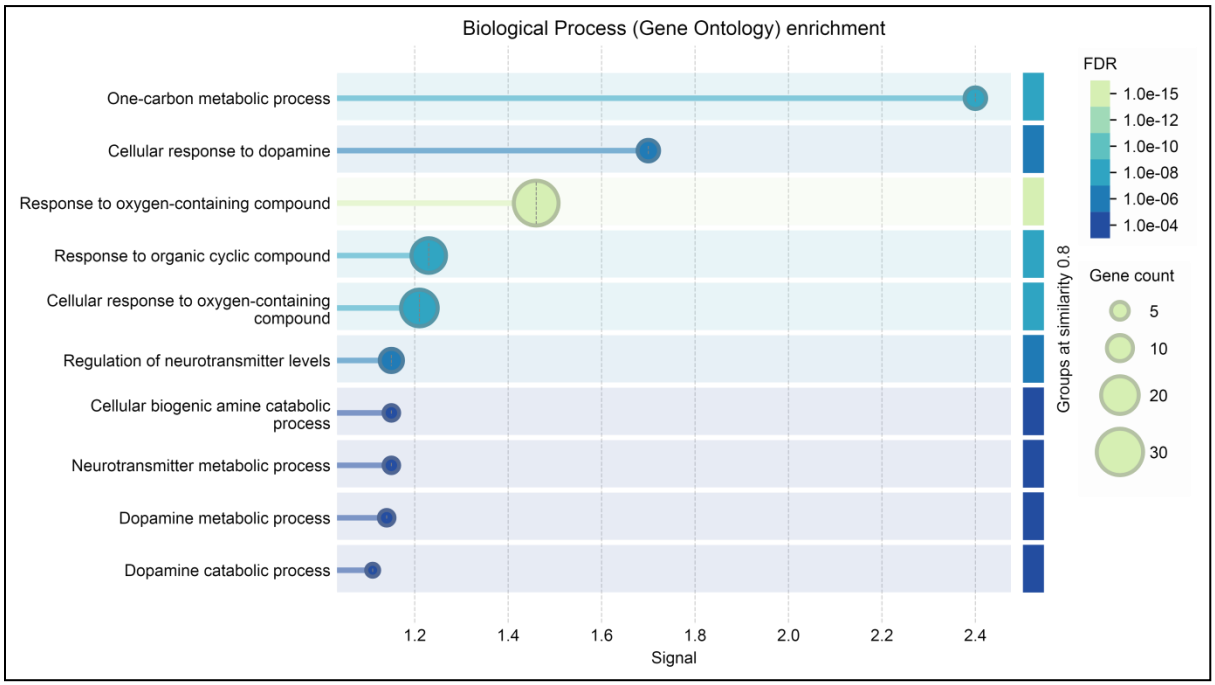


Figure 4A. Biological Process.

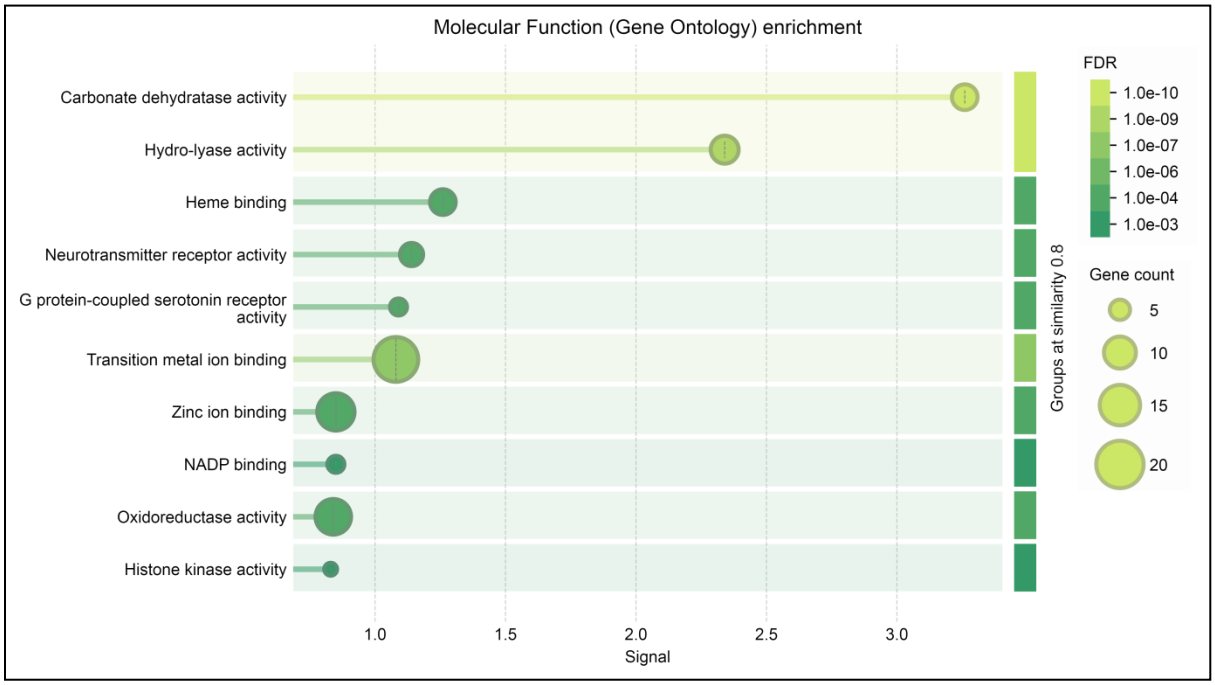


Figure 4B. Molecular Function.

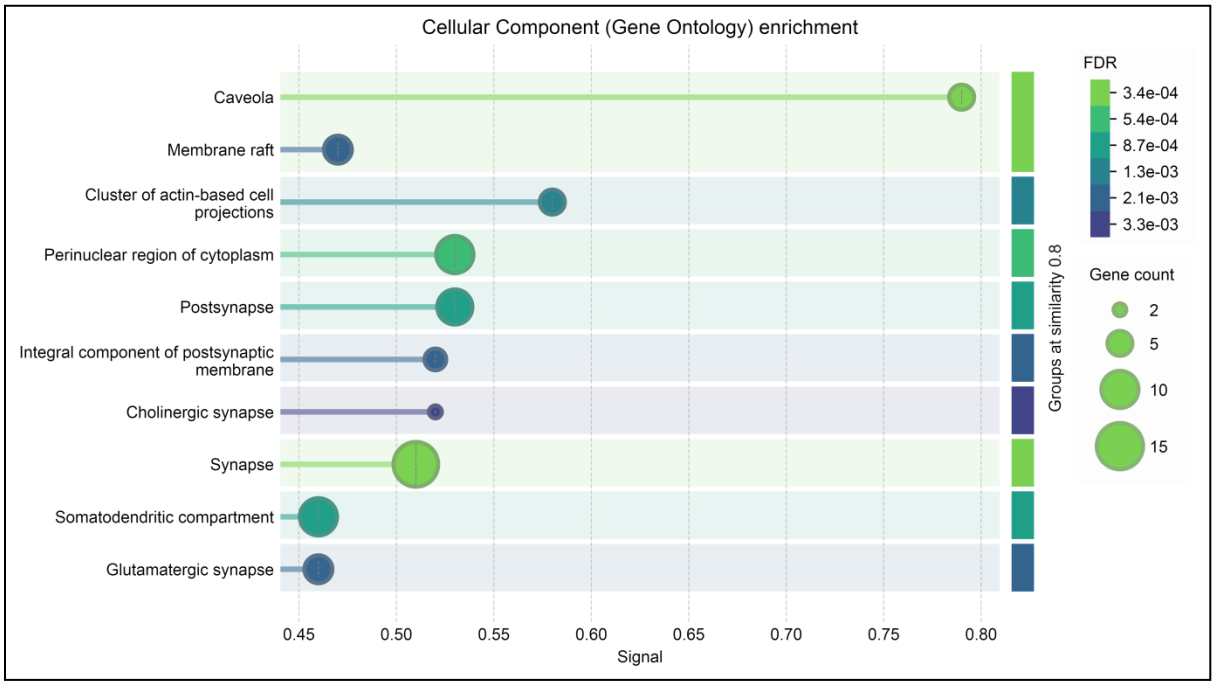


Figure 4C. Cellular Components.

Table 1. Biological Process.

Description	Observed gene count	False discovery rate
Response to oxygen-containing compound	28	7.74E-15
Response to organic substance	32	4.61E-13
Response to chemical	36	3.75E-12
Regulation of biological quality	34	1.74E-11
Cellular response to chemical stimulus	28	9.94E-10
Cellular response to oxygen-containing compound	19	5.58E-09

Table 2. Molecular Function.

Description	Observed gene count	False discovery rate
Carbonate dehydratase activity	7	2.60E-10
Hydro-lyase activity	8	1.73E-08
Ion binding	37	5.87E-08
Transition metal ion binding	18	5.87E-08
Catalytic activity	34	8.21E-07
Cation binding	30	1.40E-06

Table 3. Cellular Components.

Description	Observed gene count	False discovery rate
Caveola	5	0.0035
Synapse	14	0.0035
Perinuclear region of cytoplasm	10	0.0056
Postsynapse	9	0.0073
Cell junction	16	0.0084
Somatodendritic compartment	10	0.0104

3.5 KEGG Pathway Enrichment Analyses

The pathways associated with potential therapeutic targets for hypertension treatment were identified through KEGG pathway enrichment analysis. Signalling pathways were obtained via the string database. The top 10 signalling pathways were then visualized in a bar graph (Table 4 and Figure 5), organized by their P values in ascending order. The analysis indicated that the key targets were notably enriched in the Calcium signalling pathway (Figure 5A).

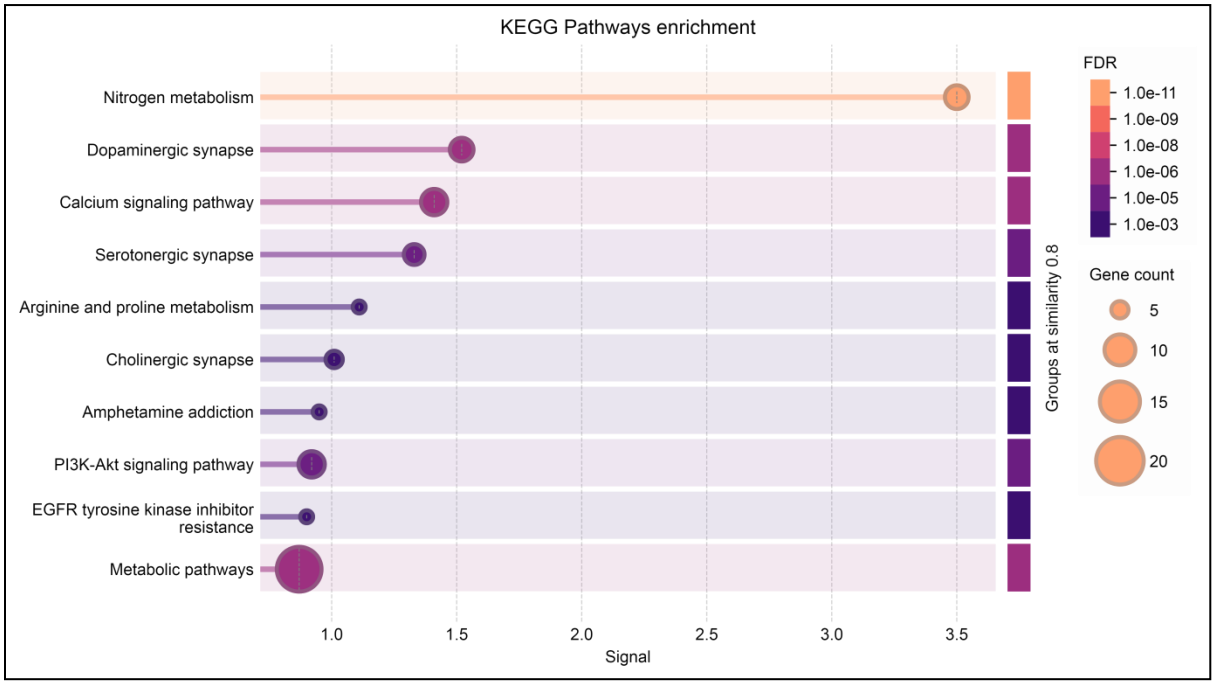


Figure 5. KEGG Pathway.

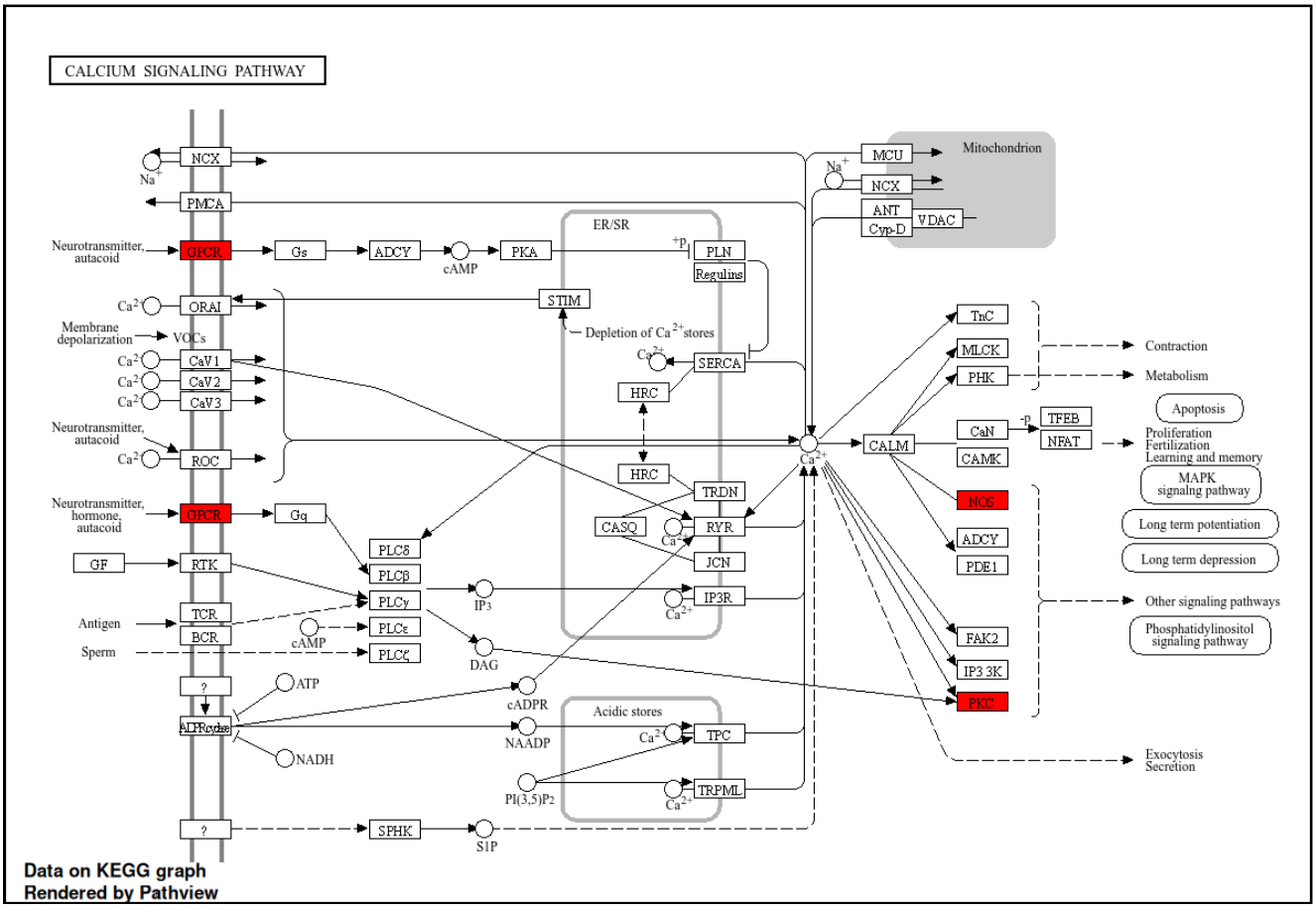


Figure 5A. Calcium signalling pathway.

3.6 Molecular Docking

Molecular docking (MD) studies of Carvacrol and Paeonol with key hypertension-associated targets, including ALB (node degree = 25) and GSK3β (node degree = 14), were performed using AutoDock Vina to evaluate binding affinities and interaction profiles. The docking analysis assessed parameters including binding affinity (kcal/mol), interacting amino acid residues. The obtained docking results demonstrated favourable ligand-protein interactions and are summarized in Table 5 and illustrated in Figure 6.

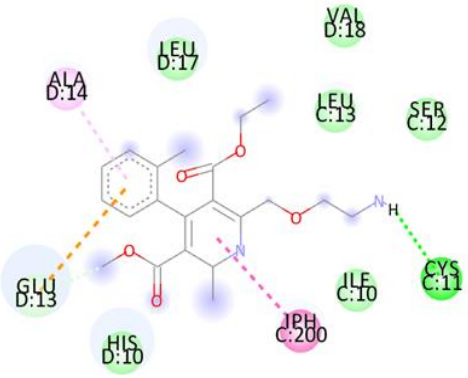
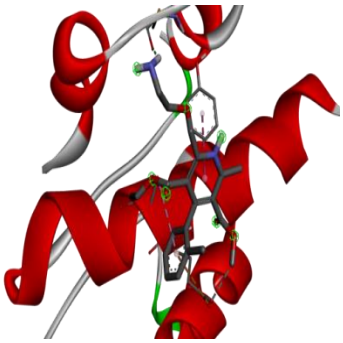
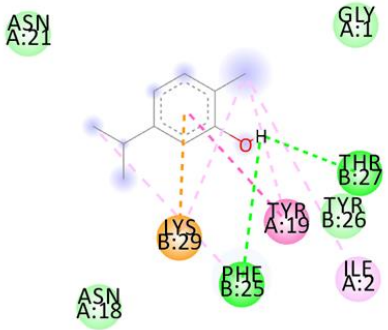
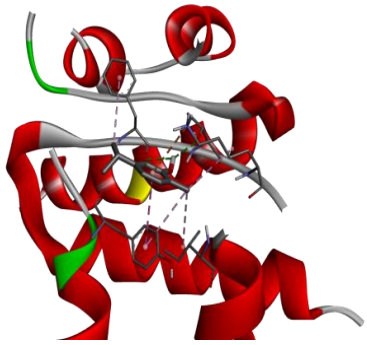
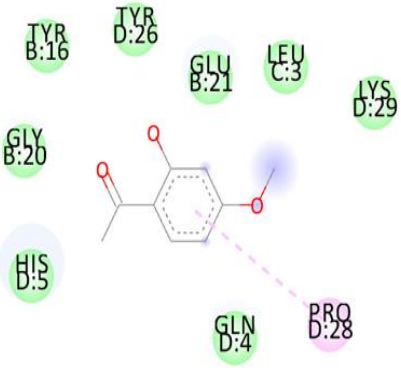
Compound/Targets	2D	3D
Amlodipine/(4J1R)		
Carvacrol /(4J1R)		
Paeonol/(4J1R)		

Figure 6. Illustrates 2D and 3D docking poses of Amlodipine, Carvacrol and Paeonol with protein GSK3β (4J1R).

Table 4. KEGG Pathway.

Description	Observed gene count	False discovery rate
Nitrogen metabolism	7	3.58E-11
Metabolic pathways	18	5.26E-07
Calcium signaling pathway	8	2.76E-06
Dopaminergic synapse	7	2.76E-06
PI3K-Akt signaling pathway	8	0.00012
Arginine and proline metabolism	4	0.00034

Table 5. Molecular docking analysis.

Sr. No.	Compound	Target Protein (PDB ID)	Binding Energy (kcal/mol)
1	Amlodipine	4N0F	-4.4
2	Carvacrol	4N0F	-4.3
3	Paeonol	4N0F	-4
4	Amlodipine	4J1R	-5.8
5	Carvacrol	4J1R	-5
6	Paeonol	4J1R	-4.8

The molecular docking study demonstrated that Carvacrol and Paeonol exhibited favourable binding affinity against hypertension-associated target proteins (4N0F and 4J1R) when compared with the standard drug Amlodipine. Among all compounds, Amlodipine showed the strongest binding affinity with docking scores of -4.4 kcal/mol against 4N0F and -5.8 kcal/mol against 4J1R. Carvacrol demonstrated comparable binding affinity with docking scores of -4.3 kcal/mol and -5.0 kcal/mol, respectively, while Paeonol exhibited moderate binding interactions with scores of -4.0 kcal/mol and -4.8 kcal/mol. The results suggest that both phytochemicals possess potential antihypertensive activity through stable interaction with target proteins involved in vascular regulation and hypertension-associated pathways.

4. Conclusion

The current study used an integrated network pharmacology and molecular docking technique to examine the therapeutic potential of Carvacrol and Paeonol against hypertension. The computational study revealed multiple common targets, biological processes, and signalling pathways linked to oxidative stress, inflammation, vascular dysfunction, and cardiovascular control. Protein-protein interaction research underlined the relevance of essential hypertension-related targets, whereas molecular docking experiments revealed Carvacrol and Paeonol had significant binding interactions and favorable binding affinities with main target proteins. The data indicate that both phytoconstituents have multi-target pharmacological activities, which may contribute to their antihypertensive properties. This work establishes a foundation for understanding the molecular processes of Carvacrol and Paeonol's antihypertensive properties and supports their prospective use as promising phytotherapeutic agents. Additional *in vitro, in vivo*, and clinical research are needed to confirm these computational discoveries and determine their therapeutic effectiveness and safety.

Author Contribution

Mir Taufique Ali contributed to data acquisition, target identification, and manuscript drafting. Shaikh Abuzar conducted molecular docking studies and pathway analysis. Dr. Shaikh Mehmood Dawood supervised the research work, edited the manuscript, and approved the final manuscript.

Funding Statement

The authors declare that no financial support or funding was received for this study.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethics Approval and Consent to Participate

This study was entirely based on computational and *in silico* methodologies including network pharmacology and molecular docking approaches. Therefore, ethical approval and informed consent were not required as no human participants or experimental animals were involved in the study.

Consent for Publication

All authors have read and approved the final version of the manuscript for publication.

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management and trust in facilitating the successful completion of this research work.

Declaration of Generative AI

During the preparation of this manuscript, generative artificial intelligence (AI)-assisted tools were utilized only for language refinement, grammatical correction, and improvement of scientific readability.

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