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Potential Molecular Targets for Hypertension in Allium schoenoprasum Identified through Network Pharmacology and Molecular Docking Approaches

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ABSTRACT

Hypertension, a major silent threat to human health, is marked by persistently elevated blood pressure. Although conventional pharmacological treatments have shown effectiveness, they are often limited by high costs and adverse effects. Recently, natural products have emerged as potential alternatives for managing hypertension. This study explored the antihypertensive potential of Allium schoenoprasum using network pharmacology and molecular docking approaches. Bioactive compounds and relevant targets were identified through comprehensive database searches. Protein-protein interaction (PPI), Gene Ontology (GO), and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to elucidate the key targets of Allium schoenoprasum. A total of 10 bioactive compounds were identified, and PPI analysis highlighted SCR, STAT3, PIK3R1, CTNBB1, and ESR1 as central targets in hypertension. Functional enrichment via GO and KEGG indicated that these targets are predominantly associated with protein binding and catalytic activities within the membrane and cytoplasm. Molecular docking further revealed that kaempferol, isorhamnetin, and quercetin are the most active compounds against hypertension. Overall, Allium schoenoprasum demonstrates promising antihypertensive effects through the combined application of network pharmacology and molecular docking strategies.

Keywords: Molecular docking, Hypertension, Network pharmacology, Allium schoenoprasum L.

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Introduction

Hypertension is recognized as one of the most serious global health threats due to its widespread prevalence. The number of individuals diagnosed with hypertension continues to rise each year, and projections estimate that nearly 2 billion people will be affected by 2025 [1]. Only a small fraction of hypertensive patients achieve effective management once the condition has manifested. The disease poses substantial health risks, including cardiovascular disorders, myocardial infarction, stroke, kidney dysfunction, intracerebral hemorrhage, end-stage organ damage, and numerous secondary complications [2], all of which significantly jeopardize patient survival and quality of life [3]. Therefore, the development of effective therapeutic agents for hypertension remains critically important.

Management of hypertension relies on both lifestyle modifications and pharmacological interventions. Antihypertensive medications, often used alongside dietary and lifestyle adjustments, have been shown to effectively lower blood pressure and heart rate, thereby reducing cardiovascular risk and mortality [4]. However, these medications are associated with several limitations, including adverse effects, high cost, and restricted access in some developing regions [5]. Consequently, there is a growing interest in identifying novel therapeutic agents, particularly those derived from natural sources, which may offer enhanced efficacy and tolerability [6].

This study focuses on Allium schoenoprasum, a member of the Amaryllidaceae family, which is widely cultivated across Asia, Europe, and North America [7]. Although its primary use is culinary [8], this plant exhibits a wide range of pharmacological activities, including anticancer, antioxidant, antibacterial, antiviral, antilithogenic, and

vasodilatory effects [7-9]. Organosulfur compounds in Allium species, such as diallyl disulfide, have been reported to reduce intercellular adhesion molecule-1 and matrix metalloproteinase-9 expression and prevent endothelial nitric oxide synthase (eNOS) inactivation, which collectively contribute to antihypertensive effects [10]. Additionally, flavonoids present in Allium schoenoprasum demonstrate blood pressure–lowering properties. For example, gallic acid reduces systolic blood pressure and oxidative stress in hypertensive rats [11], while p-coumaric acid, ferulic acid, and sinapic acid decrease ACE levels, mediating antihypertensive effects [12]. Dietary quercetin and kaempferol intake has also been linked to reduced blood pressure in hypertensive individuals [13] and isorhamnetin has been shown to inhibit TNF-α and IL-6 protein expression in vivo [14].

Given the multitude of active compounds and diverse mechanisms, harnessing natural products for hypertension treatment is complex due to their multi-target, multi-pathway actions [15]. Network pharmacology combined with molecular docking has emerged as a powerful approach to address this challenge and facilitate drug discovery [16, 17]. These techniques allow detailed analysis of drugs, protein targets, genes, and disease pathways, aligning with principles of traditional medicine, while molecular docking can validate targets predicted via network pharmacology [17]. Accordingly, this study aims to explore the potential therapeutic targets and mechanisms of Allium schoenoprasum in hypertension using network pharmacology and molecular docking, offering insights into a promising natural treatment strategy.

Materials and Methods

Compound screening

Information on potential bioactive compounds in Allium schoenoprasum was obtained from the KNApSAcK Family Databases (http://www.knapsackfamily.com/KNApSAcK/) and our previous report [18]. Compounds were filtered based on Lipinski's rule of five (no violations) and a bioavailability score greater than 0.3.

Target screening

Potential targets of the selected compounds were identified using the Swiss Target Prediction database (http://www.swisstargetprediction.ch/) by entering the SMILE code of each compound. Hypertension-related targets were retrieved from the GeneCards database (https://www.genecards.org/). Venny 2.1.0 was used to identify overlapping targets between the compound-derived targets and hypertension-associated targets, which were considered potential therapeutic targets of Allium schoenoprasum (https://bioinfogp.cnb.csic.es/tools/venny/).

Protein–protein Interaction (PPI) network construction

The interaction network among the identified target proteins was visualized using the STRING database (https://string-db.org/) by inputting the overlapping targets and selecting Homo sapiens with a high-confidence score of 0.9. The resulting PPI network was further analyzed using Cytoscape 3.9.1 (https://cytoscape.org/) to determine the most significant target proteins based on network parameters. The CytoHubba plug-in was then employed to highlight the top five key targets, with color gradients representing their relative importance according to previous analyses from STRING and Cytoscape.

Gene ontology and KEGG pathway analysis

To gain insight into the functional roles of the identified targets, Gene Ontology (GO) analysis was carried out, focusing on three categories: biological processes, molecular functions, and cellular components. Additionally, the Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.genome.jp/kegg/) was used to explore signaling pathways potentially involved in the antihypertensive effects of Allium schoenoprasum. All computational analyses were performed in RStudio, and the results were illustrated as bubble plots using the ggplot2 package [9].

Molecular docking study

The binding interactions between key bioactive compounds from Allium schoenoprasum and the top five protein targets were examined through molecular docking using PyRx 0.8 (https://pyrx.sourceforge.io/). Three-dimensional structures of the proteins were obtained from the Protein Data Bank (https://www.rcsb.org/pages/policies) with the following PDB IDs: 3F3V (SRC), 6NJS (STAT3), 2IUG

(PIK3R1), 1JDH (CTNBB1), and 7UJO (ESR1). Prior to docking, the protein structures were preprocessed in PyMol 2.5 (https://pymol.org/2/) by removing water molecules and any bound ligands [16]. The docking simulations yielded binding energy values (kcal/mol) that were recorded for subsequent analysis.

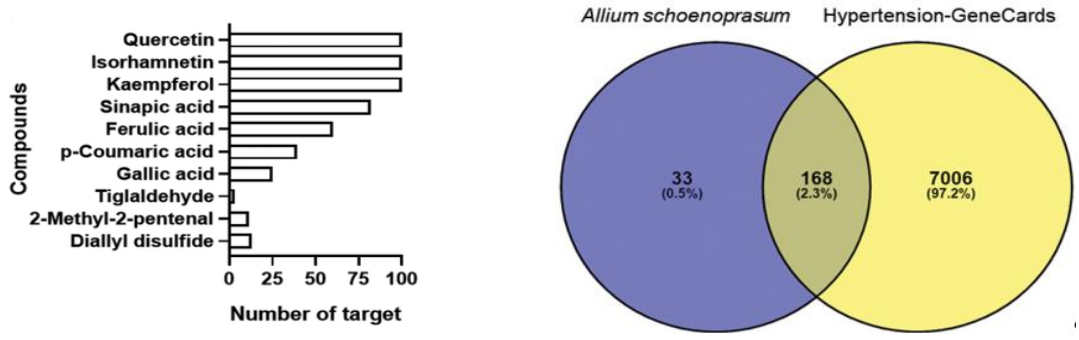
Results and Discussion

Screening of active compounds and targets

From our previous research (Iksen and Buana, 2022) and the KNApSAcK family database, 13 compounds in Allium schoenoprasum were identified as having favorable pharmacokinetic properties, including adherence to Lipinski's rule and bioavailability scores above 0.3 **(Table 1)**. Out of these, 10 compounds—Diallyl disulfide, 2-Methyl-2-pentenal, Tiglaldehyde, Gallic acid, p-Coumaric acid, Ferulic acid, Sinapic acid, Kaempferol, Isorhamnetin, and Quercetin—were predicted to interact with protein targets **(Figure 1a)**, generating a total of 201 potential protein targets. In parallel, approximately 7,174 hypertension-associated targets were retrieved from the GeneCards database. By comparing these datasets, 168 overlapping targets were identified, representing candidate targets through which Allium schoenoprasum may exert antihypertensive effects **(Figure 1b)**.

Table 1. The main compounds information from *Allium schoenoprasum* and Lipinski's rule.

Molecule	MW	Rotatable bonds	H-bond acceptors	H-bond donors	Molar refractivity	TPSA	Log P	Lipinski violations	Bioavailability score
Diallyl disulfide	146.27	5	0	0	45.19	50.6	2.49	0	0.55
2-Methyl-2-pentenal	98.14	2	1	0	30.68	17.07	1.71	0	0.55
Methyl propyl disulfide	122.25	3	0	0	36.52	50.6	2.19	0	0.55
Methyl pentyl disulfide	150.31	5	0	0	46.14	50.6	2.66	0	0.55
1-Pentanesulfenothioic acid	136.28	4	0	0	41.67	64.1	2.37	0	0.55
Tiglaldehyde	84.12	1	1	0	25.87	17.07	1.47	0	0.55
Gallic acid	170.12	1	5	4	39.47	97.99	0.21	0	0.56
p-Coumaric acid	164.16	2	3	2	45.13	57.53	0.95	0	0.85
Ferulic acid	194.18	3	4	2	51.63	66.76	1.62	0	0.85
Sinapic acid	224.21	4	5	2	58.12	75.99	1.63	0	0.56
Kaempferol	286.24	1	6	4	76.01	111.13	1.7	0	0.55
Isorhamnetin	316.26	2	7	4	82.5	120.36	2.35	0	0.55
Quercetin	302.24	1	7	5	78.03	131.36	1.63	0	0.55



a) b)

Figure 1. Distribution of potential targets of Allium schoenoprasum compounds in relation to hypertension. a. Each compound was associated with at least three predicted targets linked to hypertension, as identified through the Swiss Target Prediction database. b. Venn diagram illustrating 168 overlapping targets between

the main compounds of Allium schoenoprasum and hypertension-related targets, where yellow represents hypertension-associated targets and blue indicates compound-derived targets.

Compound–target interaction network

To examine the relationships between Allium schoenoprasum compounds and their predicted targets, a compound–target network was constructed **(Figure 2)**. The protein–protein interaction (PPI) network highlights the connections among targets, with proteins showing more interactions represented by denser lines, indicating higher connectivity within the network. This network was visualized using Cytoscape 3.9.1, where orange diamonds denote the bioactive compounds and purple ellipses correspond to hypertension-related target proteins.

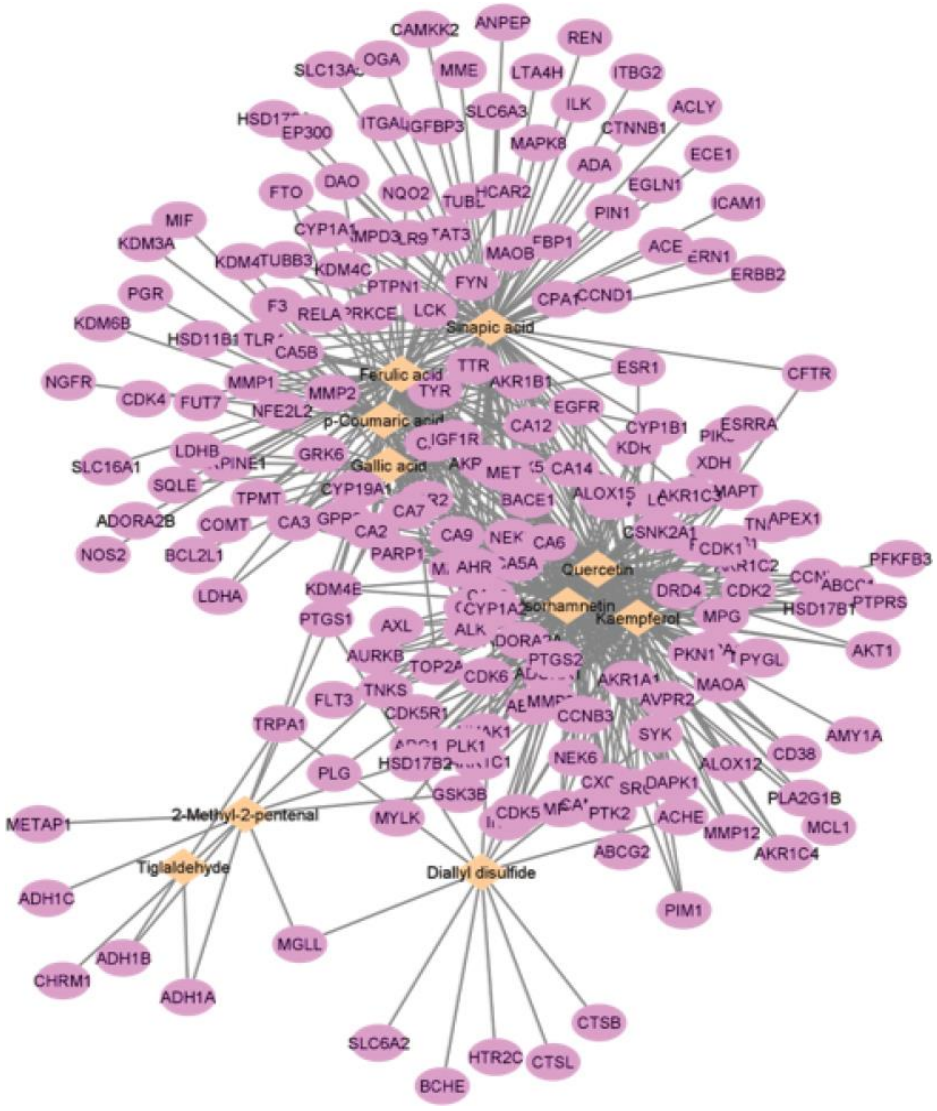
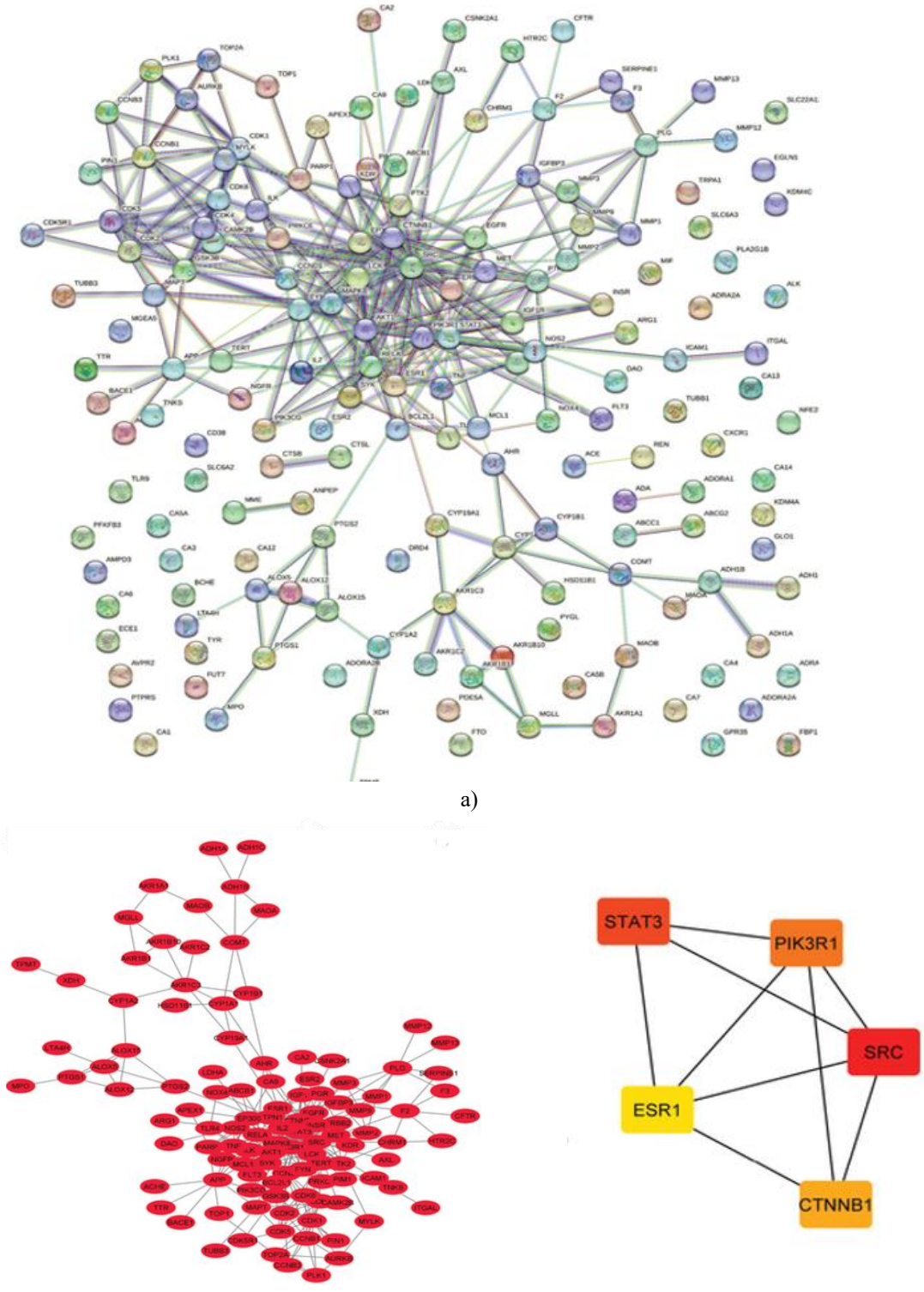


Figure 2. Network of interactions between compounds and their targets. Purple ovals indicate the protein targets, while cream-colored diamonds represent the primary bioactive compounds from Allium schoenoprasum.

Protein–protein interaction network

Protein interactions are fundamental for regulating physiological processes. To explore the functional relationships of the 168 target proteins involved in hypertension treatment, a protein–protein interaction (PPI) network was constructed using STRING 11.5 **(Figure 3a)**. Topological analysis of the network revealed 168 nodes connected by 331 edges, with an average node degree of 3.94, an average local clustering coefficient of 0.441, and a PPI enrichment p-value of less than 1.0×10^{-16}, indicating significant connectivity. The primary protein cluster within the network is illustrated in **Figure 3b**. Further analysis using the CytoHubba plug-in, based

on node degree, identified the five most central targets of Allium schoenoprasum. The interactions among these top five proteins are shown in **Figure 3c**, with SRC exhibiting the highest connectivity, followed in descending order by STAT3, PIK3R1, CTNNB1, and ESR1.



a) b) c)

Figure 3. Protein–protein interaction network. a. PPI network constructed from 168 potential targets; b. Key protein cluster identified within the network; c. The top five targets derived from the PPI analysis.

GO and KEGG enrichment analysis

To gain deeper insight into the molecular mechanisms by which the compound–target interactions of Allium schoenoprasum influence hypertension, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using RStudio. GO functional annotation was carried out in three categories: biological processes **(Figure 4a)**, molecular functions **(Figure 4b)**, and cellular components **(Figure 4c)**, with only the top ten significant terms shown. The biological process analysis indicated that the targets were mainly involved in metabolic processes and various cellular responses. Molecular function analysis revealed that protein binding and catalytic activity were predominant among the targets. Cellular component analysis showed that the majority of the targets were localized within the cytoplasm.

KEGG pathway enrichment similarly highlighted the top ten pathways associated with the antihypertensive mechanism of Allium schoenoprasum **(Figure 4d)**. These pathways primarily included cancer-related pathways, general metabolic pathways, nitrogen metabolism, HIF-1 signaling, PI3K-Akt signaling, proteoglycans in cancer, AGE-RAGE signaling in diabetic complications, endocrine resistance, microRNA-related cancer pathways, and measles-related signaling.

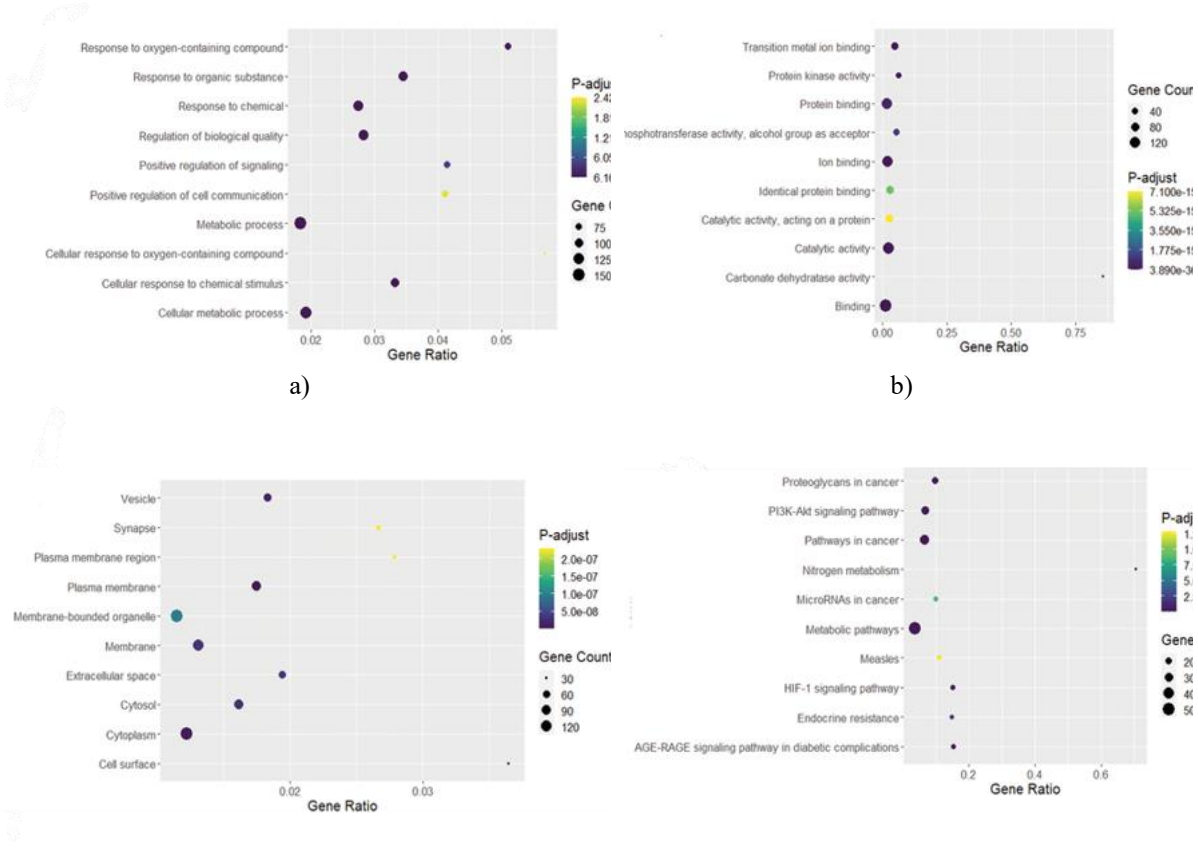


Figure 4. Enrichment analysis of Gene Ontology and KEGG pathways. A. Biological processes; B. Molecular functions; C. Cellular components; D. KEGG signaling pathways.

Molecular docking

The protein–protein interaction network identified SRC, STAT3, PIK3R1, CTNNB1, and ESR1 as the central hub targets. To investigate potential interactions between these targets and bioactive compounds from Allium schoenoprasum, molecular docking was performed using the corresponding protein structures obtained from the Protein Data Bank (PDB IDs: 3F3V, 6NJS, 2IUG, 1JDH, and 7UJO). The docking results, summarized in **Table 2**, indicate that lower binding energies correspond to stronger and more stable interactions. Among the compounds tested, kaempferol, isorhamnetin, and quercetin exhibited the most favorable binding energies across all five targets. Conversely, certain compounds, including diallyl disulfide, 2-methyl-2-pentenal, and tiglaldehyde, showed binding energies above -5 kcal/mol, suggesting weaker interactions and less stable complex formation with the target proteins [19].

Table 2.Binding energy (kcal/mol) of active compounds in *Allium schoenoprasum* and main targets.

Compounds	Binding energy (kcal/mol)				
	SRC	**STAT3**	**PIK3R1**	**CTNNB1**	**ESR1**
Diallyl disulfide	-3.9	-3.2	-3.3	-3.4	-3.8
2-Methyl-2-pentenal	-4.1	-4.1	-4.3	-3.8	-4.5
Tiglaldehyde	-3.8	-3.8	-3.9	-3.6	-4
Gallic acid	-5.6	-5.2	-5.1	-5.4	-6.4
p-Coumaric acid	-6.2	-5.5	-5.3	-5.6	-6.1
Ferulic acid	-6.4	-5.8	-5.1	-5.5	-6.2
Sinapic acid	-6.3	-6	-4.8	-5.3	-6.2
Kaempferol	-9.2	-7.2	-5.8	-7.5	-7.7
Isorhamnetin	-9.5	-7.3	-5.8	-6.5	-7.6
Quercetin	-9.4	-7.5	-5.9	-7.8	-7.5
Dasatinib (SRC inhibitor)	-8.4	-	-	-	-
Napabucasin (STAT3 inhibitor)	-	-6.6	-	-	-
LY294002 (PI3K inhibitor)	-	-	-6.4	-	-
MSAB (Beta catenin inhibitor)	-	-	-	-6.5	-
Elacestrant (ESR inhibitor)	-	-	-	-	-6.1

Hypertension, defined by a systolic blood pressure above 140 mmHg and a diastolic pressure above 90 mmHg, is often referred to as a “silent killer” due to its asymptomatic nature [1]. This chronic condition significantly increases the risk of developing kidney, heart, and cerebrovascular diseases [20]. Current standard management includes lifestyle modifications, such as reducing salt and alcohol intake, alongside pharmacological interventions, including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, alpha-blockers, and beta-blockers, which may be administered individually or in combination [21]. Despite the availability of these therapeutic options, challenges remain due to potential side effects and high costs, which can limit patient access and reduce quality of life. Therefore, the discovery of novel antihypertensive agents remains critically important.

Traditional medicine provides a rich source of potential treatments for complex diseases like hypertension and offers a basis for identifying new drug candidates [22]. In this context, network pharmacology and molecular docking have emerged as valuable tools for elucidating the mechanisms underlying multi-component, multi-target therapies and for accelerating the discovery of new antihypertensive agents [9, 23]. However, the complexity of traditional medicine, with its multiple active components and overlapping targets, often requires considerable time and resources to fully explore its pharmacological effects, limiting its broader clinical adoption.

In this study, data mining identified 13 bioactive compounds from Allium schoenoprasum with potential antihypertensive activity. Integration with hypertension-associated targets from the GeneCards database narrowed the focus to 10 compounds affecting 168 overlapping targets. Protein–protein interaction (PPI) analysis further revealed five key hub targets: SRC, STAT3, PIK3R1, CTNNB1, and ESR1. Previous research supports their relevance to hypertension: inhibition of SRC improves blood pressure and cardiac and vascular function [24, 25]; STAT3 is essential for protecting the heart from hypertensive damage, as its deficiency can impair myofibrillar structure and cardiac function, potentially leading to heart failure [26]; PIK3R1, which encodes the p85 subunit of PI3K, regulates apoptosis, inflammation, nitric oxide production, and glucose metabolism, all of which influence blood pressure [27, 28]; CTNNB1 is a key transcription factor controlling the expression of various hypertensive mediators, including angiotensinogen and ACE [29, 30]; and ESR1 promotes vasodilation by enhancing nitric oxide bioavailability and reducing oxidative stress, thereby contributing to blood pressure regulation [31].

Gene Ontology and KEGG pathway enrichment analyses indicated that these targets are primarily involved in protein binding and catalytic activity within the cytoplasm and cell membrane. Molecular docking studies confirmed strong interactions between the top five targets and the bioactive compounds, particularly kaempferol, isorhamnetin, and quercetin, highlighting their potential as multi-target antihypertensive agents. These findings

suggest that the antihypertensive effects of Allium schoenoprasum likely result from simultaneous modulation of multiple targets rather than a single-target mechanism.

However, this study has limitations, particularly regarding the reliance on data mining and in silico predictions. Future research should focus on in vivo experiments using Allium schoenoprasum extracts to further validate these mechanisms and explore their clinical potential.

Conclusion

This study utilized network pharmacology and molecular docking to investigate the antihypertensive potential of Allium schoenoprasum. PPI analysis identified SRC, STAT3, PIK3R1, CTNNB1, and ESR1 as the key targets through which the plant's bioactive compounds may exert effects. Functional enrichment analyses revealed that these targets predominantly participate in protein binding and catalytic processes within the cell membrane and cytoplasm. Molecular docking indicated that kaempferol, isorhamnetin, and quercetin are the most promising antihypertensive compounds, suggesting that Allium schoenoprasum acts via a multi-target mechanism to regulate blood pressure.

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