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IN SILICO STUDY OF ACTIVE COMPOUNDS AND PROTEIN TARGETS OF ORTHOSIPHON ARISTATUS AS ALTERNATIVE THERAPY FOR HYPERTENSION: NETWORK PHARMACOLOGY AND DOCKING

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ABSTRACT

Hypertension poses a significant global health burden, prompting exploration into alternative treatments. This study investigates the pharmacological network of Orthosiphon aristatus, aiming to uncover its therapeutic potential for hypertension. We compiled data on Orthosiphon aristatus chemical constituents and predicted potential targets for its key components. Through screening processes utilizing the Gencard database, active compounds and protein targets were identified. We examined protein target similarities between Orthosiphon aristatus and hypertension, constructing a network illustrating the relationships between active compounds and target genes. Additionally, we conducted GO function analysis and KEGG pathway enrichment to elucidate Orthosiphon aristatus role in hypertension. Notably, TP53 exhibited the highest degree of centrality, while Scutellarein and aurantiamide acetate displayed the highest affinities in molecular docking with TP53. These findings offer novel insights into Orthosiphon aristatus' potential as an adjunctive therapy for hypertension and contribute to the advancement of pharmacological interventions in this domain.

KEYWORDS *Hypertension, Orthosiphon aristatus, Network Pharmacology, Docking*

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INTRODUCTION

Hypertension is the most common and frequently occurring chronic non-communicable disease. It also poses a significant global economic burden and is recognized as an important risk factor for cardiovascular diseases (Guo et al., 2020). Observational data from the Framingham study indicate that individuals aged 55 to 60 have a 90% lifetime risk of developing hypertension, explaining why global population aging trends are a significant contributor to the increasing prevalence of hypertension worldwide (Benetos et al., 2019). Hypertension, known as an increase in blood pressure, is a common cardiovascular disorder that potentially increases the risk of other serious comorbidities such as myocardial infarction, stroke, chronic kidney failure, and diabetes (Lago et al., 2007; Oparil et al., 2018). Less than half of hypertension patients are aware of their condition, and many others are aware but untreated or inadequately treated, despite successful hypertension treatment reducing the global burden of disease and mortality (Oparil et al., 2018).

In various regions of Indonesia, there are numerous plant species that can be utilized as raw materials to produce modern and traditional medicines. The Indonesian community applies the use of plants with medicinal properties as a step to address various health problems (Yulianti, 2015). One of the medicinal plants widely used in Asia is *Orthosiphon aristatus* (Blume) Miq (Abdullah et al., 2020). *Orthosiphon aristatus* is a traditional folk medicine widely used in Southeast Asia due to its various pharmacological effects, including antioxidant, antitumor, and hypoglycemic activities (Ohashi et al., 2000; Samidurai et al., 2020).

Orthosiphon aristatus is commonly used as ethnomedicine to treat rheumatism, hypertension, tonsillitis, epilepsy, male disorders, gonorrhea, syphilis, kidney stones, gallstones, lithiasis, edema, fever, eruptions, influenza, and hepatitis (Arafat et al., 2008; Awale et al., 2004; Nguyen et al., 2004). This plant is distributed across India, China, Myanmar, Cambodia, Thailand, Malaysia, and Vietnam. In traditional medicine, this plant has been used to treat acute and chronic nephritis, cystitis, urolithiasis, and rheumatism (Chi et al., 2012). The active constituents found in *Orthosiphon aristatus* are polyphenols, terpenoids, and sterols (Hollman & Katan, 1999; Tezuka et al., 2000).

In this study, we aim to elucidate the pharmacological network of *Orthosiphon aristatus* in the context of hypertension by employing in silico methods. By identifying active compounds and their respective protein targets, along with pathway enrichment and functional analysis, we strive to uncover the underlying molecular mechanisms and potential therapeutic effects of *Orthosiphon aristatus*. By integrating these data, we hope to provide a comprehensive understanding of how this traditional medicinal plant can be leveraged as an alternative therapy for hypertension.

RESEARCH METHOD

Identification and Screening of Active Compounds

The active compounds present in *Orthosiphon aristatus* were selected from the website http://www.knapsackfamily.com/knapsack_core/top.php, Tung et al., (2022), Chassagne et al., (2018), Matusbara et al., (1999), Shafaei et al., (2018), Faramayuda et al., (2021). The screening process involved evaluating the physicochemical properties and pharmacokinetics of the compounds using the pkCSM database (https://biosig.lab.uq.edu.au/pkcsm/prediction) and ProTox (https://tox-new.charite.de/protox_II/index.php?site=compound_input). Screening was performed by examining Lipinski's rule of five and the toxicological values of the identified compounds (Lipinski, 2004; Mardianingrum et al., 2021)

Identification of Protein Targets

The protein targets of the compounds found in *Orthosiphon aristatus* were identified through the GeneCards database (https://www.genecards.org/). From the various identified targets, the targets were sorted based on the GIFtS values, and the top 25 targets with the highest GIFtS values for each compound were selected (Yang et al., 2019)

Prediction of Hypertension Targets

The identified targets of the studied compounds were compiled into one list, and duplicates were removed. Hypertension targets were obtained from the GeneCards database (https://www.genecards.org/).

Determination of Protein Target Similarities Between *Orthosiphon aristatus* and Hypertension

Protein target similarities were determined by comparing the compound targets with hypertension targets using the Venny 2.1 platform (https://bioinfogp.cnb.csic.es/tools/venny/). The overlapping targets were selected to construct the relationship between the compounds and targets (Oliveros, 2007).

Representasi dan interaksi protein-protein

The Search Tool for the Retrieval of Interacting Genes (STRING) was used to search for compound-target interactions using the STRING database (http://string-db.org) with the species set to Homo sapiens, a "high confidence >0.7" score, and FDR stringency set to "HIGH: 1%" (Crosara et al., 2018).

Construction of the Network of Relationships Between Compounds and Target Genes

All selected targets from the identified compounds were compiled into Microsoft Excel. The relationships between the active compounds in the plant and the protein targets were then constructed using the CytoScape application (https://cytoscape.org/).

GO Function and KEGG Pathway Enrichment Analysis

GO function and KEGG pathway analysis were performed using ShinyGO 0.80 (http://bioinformatics.sdstate.edu/go/) on the active components of

Orthosiphon aristatus selected from the merged Hypertension targets. The selected genes were Homo sapiens with an FDR cutoff of 0.05, pathway size 2 to 2000, and 30 pathways to show (Ge et al., 2020).

Molecular Docking

The ligand structures were sourced from PubChem (https://pubchem.ncbi.nlm.nih.gov), while protein targets were obtained from RCSB (https://www.rcsb.org/). The docking process utilized Autodock Vina integrated with PyRx, and visualization was conducted using Discovery Studio software. Prior to docking, ligands and water molecules were prepared by removing the latter and ensuring appropriate hydrogenation and charge assignment.

RESULT AND DISCUSSION

Table 1. Physicochemical Properties of Orthosiphon A Compounds

Compound	Molecular Weight	Log P	Rotatable Bonds	H Acceptors	H Donors
1,8-Cineol	154.253	2.744	0	1	0
3′,4′,5,6,7-pentamethoxyflavone	372.37	3.503	6	7	0
3-hydroxy-5,7,4-trimethoxyflavone	328.32	3.191	4	6	1
5,6-dihydroxy-7,3′,4′-trimethoxyflavone	344.319	2.897	4	7	2
5-Hydroxy-6,7,3',4'-tetramethoxyflavone	358.346	3.2	5	7	1
Aurantiamide acetate	444.531	3.3183	10	4	2
baicalein	270.24	2.5768	1	5	3
caffeic acid	180.159	1.1956	2	3	3
Caftaric acid	312.23	-0.4471	6	7	5
chrysin	254.241	2.8712	1	4	2
Cirsimaritin	314.293	2.8884	3	6	2
Cryptotanshinone	296.366	3.4433	0	3	0
Danshensu	198.174	0.0858	3	4	4
Eugenol	164.204	2.1293	3	2	1
Eupatorin	344.319	2.897	4	7	2
Limonene	136.238	3.3089	1	0	0
N-feruloyltyramine	313.353	2.4785	6	4	3
oroxylin A	284.267	2.8798	2	5	2
p-Cymene	134.222	3.11842	1	0	0
rosmarinic acid	360.318	1.7613	6	7	5
scutellarein	286.239	2.2824	1	6	4
Scutellarein 5,6,7,4'-tetramethyl ether	342.347	3.4944	5	6	0
sinensetin	372.373	3.503	6	7	0
Tanshinone IIA	294.35	4.24792	0	3	0
α-Pinene	154.253	2.6698	4	1	1
β-Caryophyllene	204.357	4.7252	0	0	0

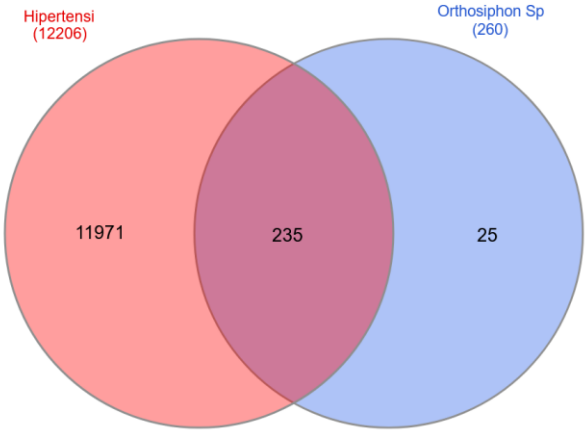


Fig 1. Venn Diagram of Hypertension Targets with Orthosiphon A Targets.

Tabel 2. Farmakokinetika Senyawa Aktif *Orthosiphon A*

Compound	Water solubility	Intestinal absorption (human)	VDss (human)	BBB Permeability	CYP 2D6 Substrate	CYP 2D6 Inhibitior	Renal OCT2 Substrate	Total Clearance	Oral Rat Acute Toxicity (LD50)	LD50	Toxicity Class
1,8-Cineol	-2.63	96.505	0.491	0.368	No	No	No	1.009	2.01	2480mg /kg	5
3′,4′,5,6,7-Pentamethoxyflavone	-4.682	98.578	-0.188	-1.008	No	Yes	No	0.771	2.503	5000mg /kg	5
3-hydroxy-5,7,4-Trimethoxyflavone	-3.995	95.732	-0.253	-0.715	No	No	Yes	0.75	2.129	4000mg /kg	5
5,6-dihydroxy-7,3′,4′-Trimethoxyflavone	-3.366	89.136	-0.044	-0.821	No	No	No	0.639	2.179	4000mg /kg	5
5-Hydroxy-6,7,3',4'-Tetramethoxyflavone	-4.134	95.667	-0.21	-0.924	No	No	No	0.716	2.299	5000mg /kg	5
Aurantiamide acetate	-4.098	94.997	-0.016	-0.283	No	Yes	No	0.619	1.961	550mg /kg	4
baicalein	-3.302	94.268	-0.004	-1.061	No	Yes	No	0.252	2.325	3919mg /kg	5
caffeic acid	-2.33	69.407	-1.098	-0.647	No	No	No	0.508	2.383	2980mg /kg	5
Caftaric acid	-2.541	9.399	-0.919	-1.233	No	No	No	0.449	2.174	3800mg	5

										/kg	
chrysin	-3.538	93.761	0.403	0.047	No	Yes	No	0.405	2.289	3919mg /kg	5
Cirsimaritin	-3.481	93.987	0.001	-0.59	No	Yes	No	0.587	2.254	4000mg /kg	5
Cryptotanshinone	-3.79	98.144	0.109	0.245	No	No	No	0.845	2.113	8000mg /kg	6
Danshensu	-2.18	41.772	-0.63	-0.876	No	No	No	0.444	2.22	2000mg /kg	4
Eugenol	-2.25	92.041	0.24	0.374	No	No	No	0.282	2.118	1930mg /kg	4
Eupatorin	-3.318	99.538	-0.025	-0.749	No	No	No	0.639	2.246	4000mg /kg	5
Limonene	-3.568	95.898	0.396	0.732	No	No	No	0.213	1.88	4400mg /kg	5
N-feruloyltyramine	-3.292	90.23	0.128	-0.715	No	No	No	0.27	1.873	500mg /kg	4
oroxylin A	-3.434	94.344	0.175	-0.117	No	Yes	No	0.313	2.412	4000mg /kg	5
p-Cymene	-4.081	93.544	0.697	0.478	No	No	No	0.239	1.827	3mg /kg	1
rosmarinic acid	-3.059	32.516	0.393	-1.378	No	No	No	0.25	2.811	5000mg /kg	5
scutellarein	-3.156	66.687	0.587	-1.398	No	No	No	0.47	2.452	3919mg /kg	5
Scutellarein 5,6,7,4'-tetramethyl ether	-4.462	98.35	-0.112	-0.586	No	No	Yes	0.785	2.4	4000mg /kg	5
sinensetin	-4.682	98.578	-0.188	-1.008	No	Yes	No	0.794	2.503	5000mg /kg	5
Tanshinone IIA	-4.494	96.253	0.325	0.302	No	Yes	No	0.821	2.649	1190mg /kg	4
α-Pinene	-2.612	93.163	0.152	0.598	No	No	No	0.446	1.704	4400mg /kg	5
β-Caryophyllene	-5.555	94.845	0.652	0.733	No	No	No	1.088	1.617	5300mg /kg	5

Active Compound Components and Targets of *Orthosiphon aristatus* and Disease Targets

The active compounds of *Orthosiphon aristatus* were sourced from various references, totaling 70 compounds: 13 from the Knapsack database with Jamu, 14 from Tung et al., 6 from Chassagne et al., 4 from Matusbara et al., and 29 from Faramayuda et al. Tung et al., 2022, Chassagne et al., 2018, Matusbara et al., 1999, Shafaei et al., 2018, Faramayuda et al., 2021.). Targets for these compounds were identified using GeneCards, selecting the top 25 targets per compound. Screening based on pharmacokinetics and Lipinski's Rule of Five (molecular weight <500, Log P <5, H-bond acceptors <10, H-bond donors <5) resulted in 28 predicted compounds, as shown in Table 1.

Hypertension Targets and Compound Target Screening

Hypertension targets were obtained from GeneCards, totaling 12,206 targets. These targets were then compared with compound targets using a Venn diagram, as shown in Figure 1, resulting in 235 common targets. The results indicate that the common targets between the compound and the disease are essential for understanding the pharmacological effects of *Orthosiphon aristatus*.

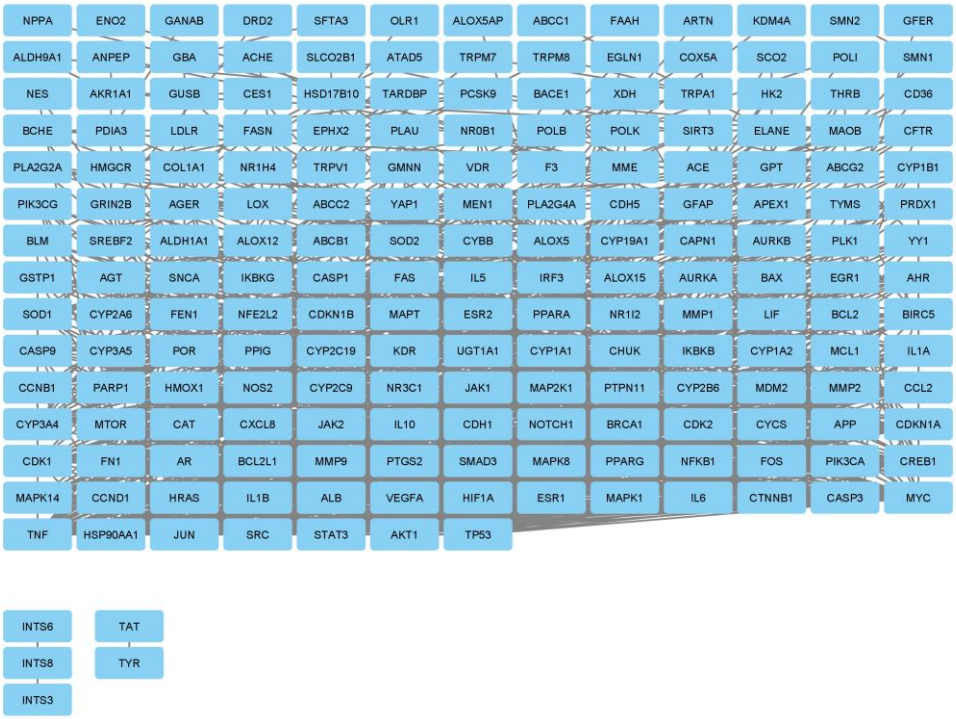


Fig 2. Protein-Protein Interactions of Active Compounds in Orthosiphon A

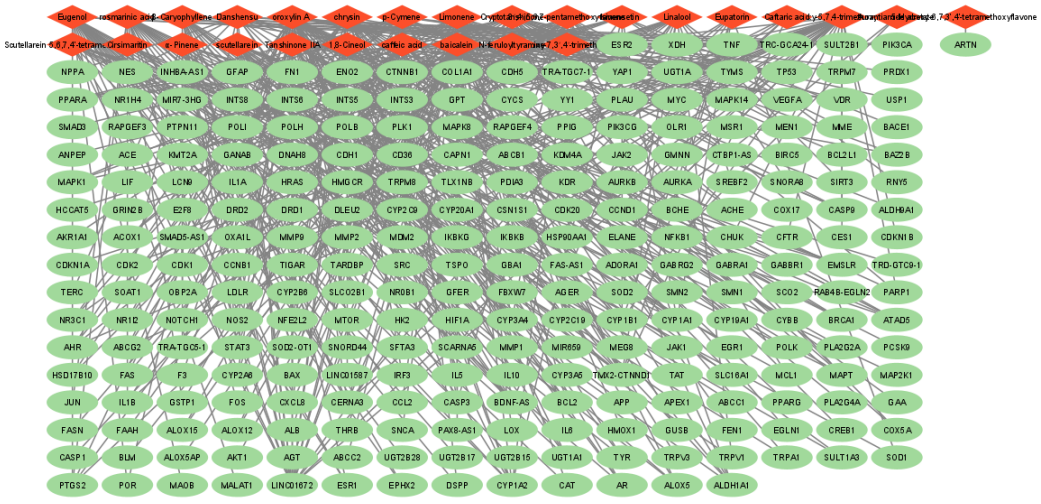


Fig 3. Pharmacological Network of Orthosiphon A's Active Compound Targets

Table 3. Degree of Protein-Protein Interaction

Protein	Degree	Protein	Degree
TP53	75	IL6	42
AKT1	63	MAPK1	42
STAT3	55	ESR1	38
SRC	54	HIF1A	37
JUN	53	VEGFA	36
HSP90AA1	50	ALB	35
TNF	47	HRAS	35
MYC	46	IL1B	35
CTNNB1	44	CCND1	32
CASP3	44	MAPK14	31

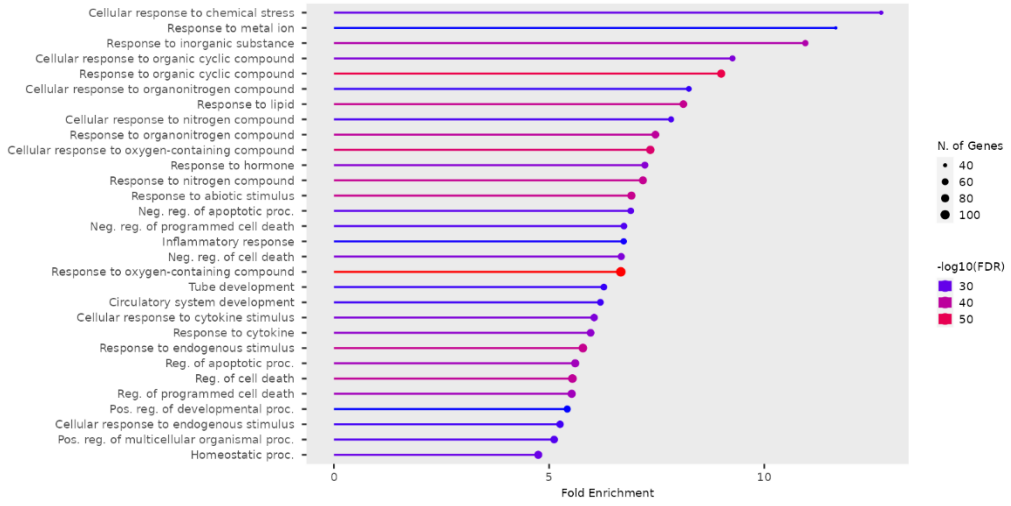


Fig 4. GO Bio Proses

Construction of Protein-Protein Interactions

We filtered and predicted the network of protein-protein interactions using STRING and downloaded the interaction results in TSV format. These interactions were then visualized using Cytoscape 3.9.1, resulting in a network comprising 235 proteins with 194 nodes and 1386 edges. The compound-target interaction network was constructed using Cytoscape 3.9.1 for *Orthosiphon aristatus* and hypertension targets. Details are shown in Figure 3. The *Orthosiphon aristatus* network includes 28 compounds with 260 known targets, out of which 235 compounds were found to have anti-hypertensive properties in the network. The interaction analysis revealed 287 nodes and 500 edges, with nodes representing *Orthosiphon aristatus*. Within this network, several targets are shared among multiple compounds. The three compounds with the highest network connections are Oroxolyn A, Baicelin, and 3-Hydroxy-5,7,4-trimethoxcyflavone.

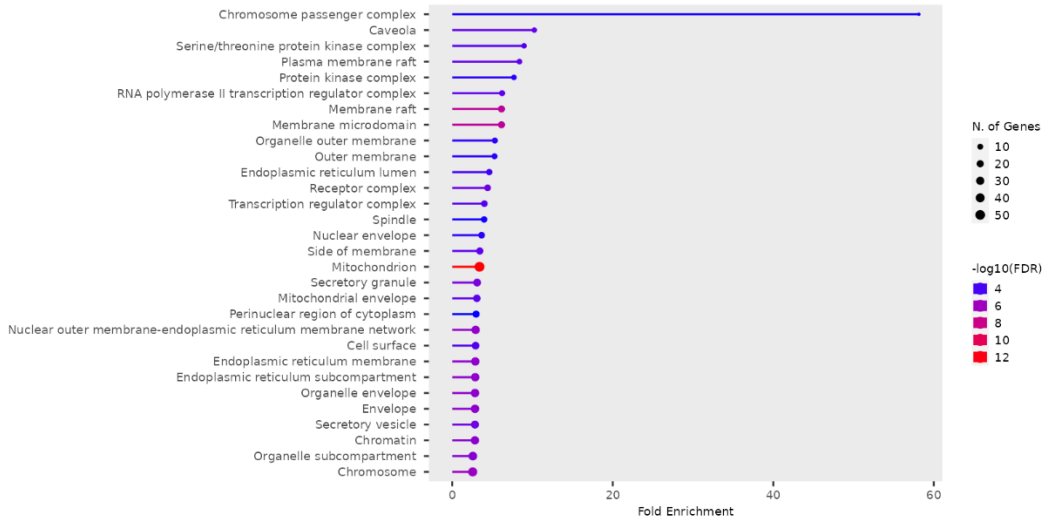
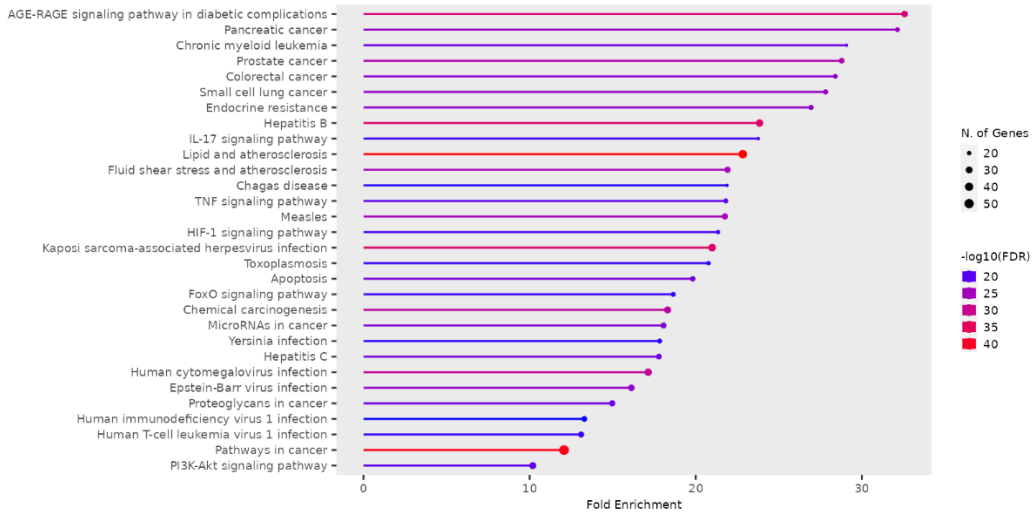


Figure 5. GO Cellular Component



Figue 6. KEGG Top 30

Pathway Enrichment Analysis for Key Target Analysis

To further study the molecular mechanisms of Orthosiphon aristatus, GO (Gene Ontology) analysis and pathway enrichment of 235 candidate targets were conducted using the KEGG database on Shiny GO. The GO analysis results are explained in terms of biological processes (BP), cellular components (CC), and KEGG pathways. The selected KEGG pathways are Lipid Metabolism and Atherosclerosis, as these pathways provide an overall representation of the processes underlying hypertension.

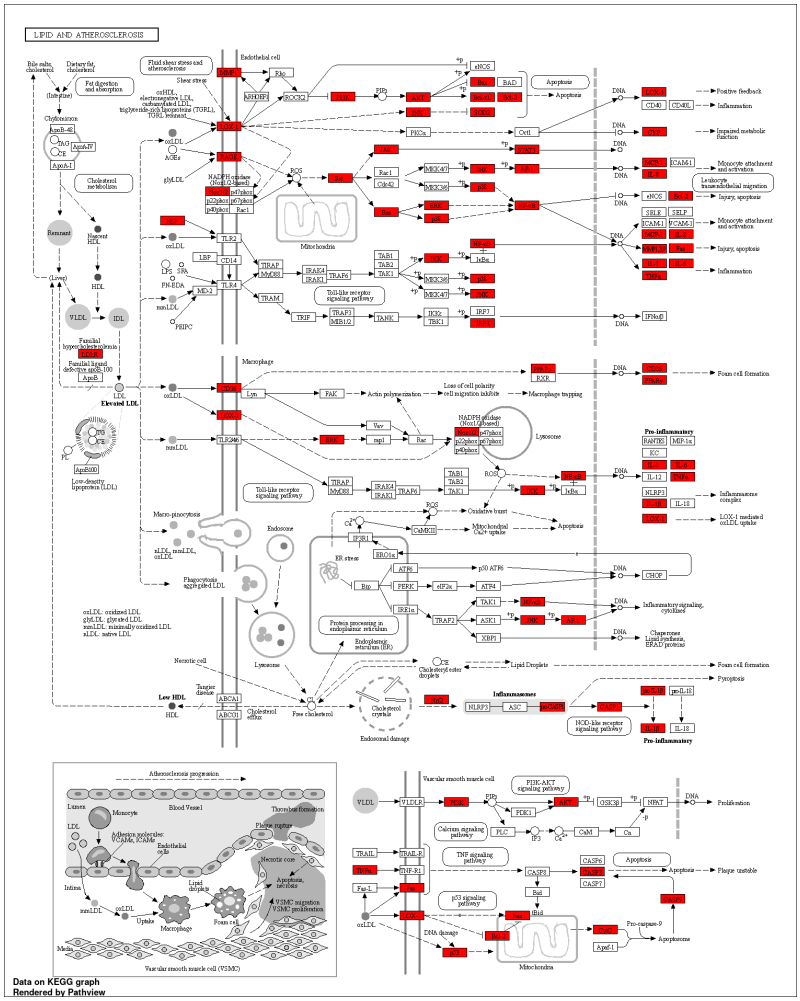


Figure 7. Proses KEGG Ateroskelorosis

Table 4. Molecular docking TP53 (1KZY)

Compound	CID	Binding Afinity (kcal/mol)	H-Bond
1,8-Cineol	2758	-4.7	-
3′,4′,5,6,7-pentamethoxyflavone	145659	-6.4	-
3-hydroxy-5,7,4-trimethoxyflavone	624831	-6.9	ASN1845, VAL172, ARG174, GLN1841, LEU1840, ASN1842, THR211
5,6-dihydroxy-7,3′,4′-trimethoxyflavone	10020367	-6.9	HIS179, HIS178, SER96, THR170, ARG213
5-Hydroxy-6,7,3',4'-tetramethoxyflavone	152430	-6.8	ARG1844, ALA1714, GLN1839, GLN1841, ARG174, GLU180, ARG175
Aurantiamide acetate	124319	-8.0	ARG1744, ASN1842, ARG174
baicalein	5281605	-7.7	HIS178, MET243, ASN239
caffeic acid	689043	-5.9	ASP1833, GLN1718, CYS176
Caftaric acid	6440397	-6.2	MET243, HIS178, HIS179, ASP1807
chrysin	5281607	-7.4	HIS178, MET243
Cirsimaritin	188323	-7.9	ASP1833, SER241, HIS178, ASN239, MET243

Cryptotanshinone	160254	-7.8	GLN1718
Danshensu	11600642	-5.6	ALA1714, GLN1839, GLN1841, GLY8244, GLU180, ARG175
Eugenol	3314	-5.2	LEU1728, LEU1840
Eupatorin	97214	-7.3	SER896, ARG213, ARG174, ASN184
Limonene	22311	-4.9	-
N-feruloyltyramine	5280537	-6.8	GLN1718
oroxylin A	5320315	-7.6	MET243, HIS178, ASN239
p-Cymene	7463	-4.9	-
rosmarinic acid	5281792	-7.0	VAL172, GLU171, ARG175, GLU180, ASN1845, ALA1714, LEU1715
scutellarein	5281697	-8.0	ASP1833, HIS178, MET243, ASN239
Scutellarein 5,6,7,4'-tetramethyl ether	96118	-7.2	ASN239, HIS178, ARG181, ASP1833, GLN1718
sinensetin	145659	-6.4	MET243, GLN1718
Tanshinone IIA	164676	-7.9	ARG174

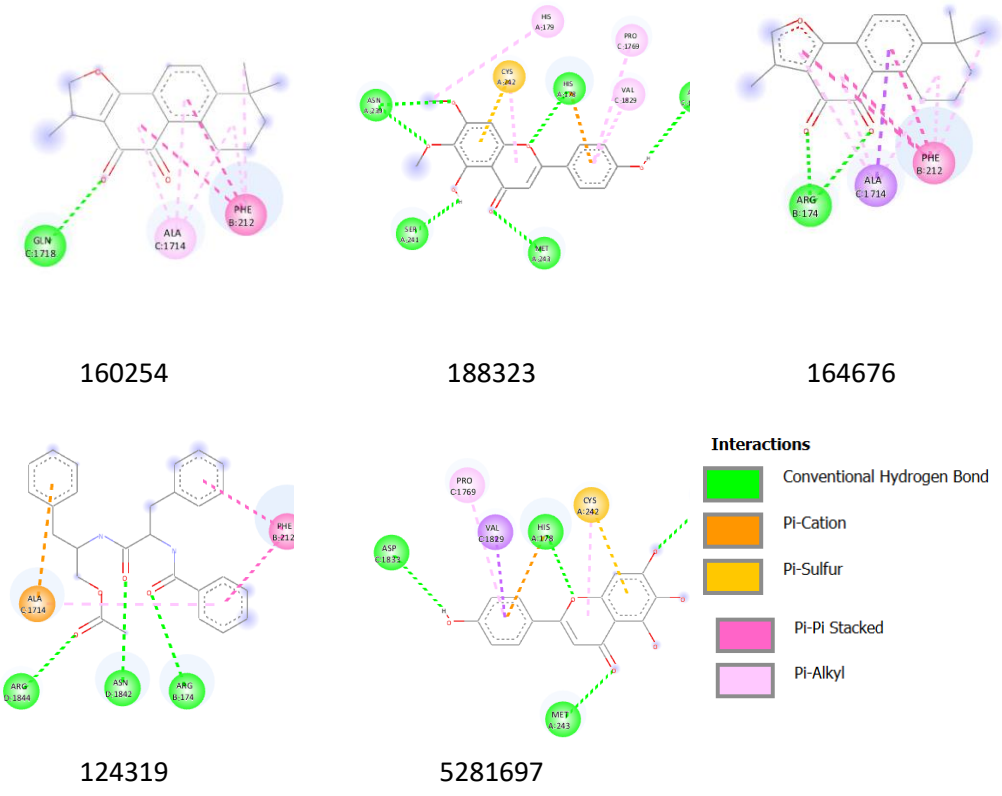


Fig 8. Visualization of molecular docking (TOP 5)

Discussion

This study used a computational systems pharmacology approach consistent with network link prediction and statistical analysis to investigate the interactions of active compounds from *Orthosiphon aristatus* with hypertension. (Wang et al.,

2018). The active compounds were screened by examining their physicochemical properties and pharmacokinetic data. The initial data was filtered using Lipinski's rule of five (LRo5) criteria: molecular weight < 500, hydrogen bond acceptors < 10, LogP < 5, and hydrogen bond donors < 5. These parameters reflect the basic characteristics of molecules, particularly their pharmacokinetic properties. (Lipinski et al., 2001). In the selection of physicochemical properties, assessment is based on the molecular weight of the compounds. A larger molecular weight hinders the absorption and distribution of the compounds within the body. Meanwhile, the Log P value indicates the partitioning of a compound between octanol and water. The higher the Log P value, the more nonpolar the compound, which in turn makes it more difficult for the compound to be absorbed in the intestines (Van de Waterbeemd, 2007). Additionally, the physicochemical properties filtered include the hydrogen bond donor value. In this case, the hydrogen bond donor value should not exceed 5, while the hydrogen bond acceptor value must be less than or equal to 10. Values that do not meet these criteria or exceed them will reduce the oral bioavailability of the candidate compounds. (Corbett et al., 2021).

The screening results of the active compounds from *Orthosiphon aristatus* yielded 28 compounds, which were then analyzed using PKCSM to evaluate their pharmacokinetics. In terms of absorption, a crucial parameter is the Human Intestinal Absorption (HIA). The higher a compound's absorption rate, the better its bioavailability. High bioavailability increases the likelihood of the compound binding to its target (Han et al., 2019). According to **Table 2.** 27 compounds exhibited high HIA values, except for Caftaric acid, which had an HIA value of 9.39%. Another important profile is distribution, which is assessed by the volume of distribution (VDss). A VDss value is considered low if it is < -0.15, and high if it is > 0.45.(Wadanambi & Mannapperuma, 2021). Another crucial parameter in pharmacokinetics is metabolism. Based on ADMET prediction results, the active compounds were evaluated for their roles as substrates and inhibitors of CYP2D6. The data in Table 2 reveal that none of the compounds act as CYP2D6 substrates, though several function as CYP2D6 inhibitors. The CYP2D6 enzyme is pivotal in the metabolism of approximately 25% of all clinically utilized drugs. Consequently, inhibition of CYP2D6 can lead to interactions with drugs that are CYP2D6 substrates. Given that patients frequently use multiple medications concurrently, drug-drug interactions must be carefully considered when predicting the appropriate dosage of CYP2D6 substrate drugs, such as the antidepressants bupropion, fluoxetine, and paroxetine. (Molden & Jukić, 2021).

Another crucial parameter assessed in ADMET analysis is excretion. Based on predictions, nearly all compounds derived from *Orthosiphon aristatus* are not substrates of OCT2, a primary transporter responsible for the renal secretion of cationic drugs (Motohashi & Inui, 2013). his indicates these compounds do not interfere with the excretion of endogenous substances into urine. Furthermore, total clearance values range from 0.203 to 1.088 log ml/min/kg. Clearance is widely recognized as a pivotal pharmacokinetic parameter as it influences various aspects such as drug half-life, oral bioavailability, and dosing regimen, thereby crucial in understanding the elimination kinetics of compounds from the body. (Smith et al.,

2019). The final parameter assessed in pharmacokinetic analysis using PKCSM is toxicity. The chosen toxicity data includes the acute LD50 values in rats and their corresponding toxicity classes. According to **Table 2**, the LD50 values range from 1.617 to 2.811, indicating generally high toxicity levels for most compounds, except for p-Cymene which exhibits an LD50 of 3 mg/kg. This categorizes p-Cymene into toxicity class 1, signifying its substantial toxicity based on both its toxicity class and LD50 value of 3 mg/kg (Guengerich, 2011).

Protein-protein interactions among targets are delineated in Table 3. Notably, TP53 (Tumor Protein P53) exhibits significant downregulation in the lungs of a hypoxia-induced pulmonary hypertension rat model (Wakasugi et al., 2019). AKT1 (AKT Serine/Threonine Kinase 1) governs blood pressure by modulating vascular relaxation through eNOS phosphorylation and subsequent nitric oxide production (Ha et al., 2011). STAT3 (Signal Transducer and Activator of Transcription 3) maintains normal cardiac myofibril morphology; its deficiency can impair cardiac function in hypertensive hearts due to myofibrillar structural damage and resultant remodeling, potentially precipitating heart failure (Zouein et al., 2013). SRC (SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase) plays a pivotal role in smooth muscle cell proliferation and migration in pulmonary arterial smooth muscle cells (PASMCs), influencing pulmonary vascular hemodynamics and remodeling in experimental pulmonary hypertension, and affects the expression and regulation of the Src kinase family (Pullamsetti et al., 2012).

The interaction between targets and compounds reveals notable findings. Oroxylin A demonstrates high affinity towards multiple targets and has been extensively studied for its in vivo antihypertensive effects (Sajeev et al., 2022). Similarly, 3-hydroxy-5,7,4-trimethoxyflavone shows significant connectivity with hypertension targets. Tanshinone IIA ranks third in compound affinity with hypertension targets. Research by Chan et al., (2011) demonstrates its efficacy in reducing blood pressure in rats, acting as the active principle of danshen and inducing vasodilation through ATP-sensitive K+ channels to lower [Ca2+]. Eugenol also exhibits strong connectivity with hypertension targets, lowering blood pressure in rats by dilating cerebral arteries through multi-modal inhibition of Ca2+ channels (Peixoto-Neves et al., 2014, 2015). Furthermore, rosmarinic acid reduces blood pressure in animal models by inhibiting angiotensin-converting enzyme (ACE) (Ferreira et al., 2018; Li QL et al., 2008; Prasannarong et al., 2019).

Enrichment analysis of KEGG pathways and GO functions reveals that targets of *Orthosiphon aristatus* for antihypertensive treatment are prominently associated with lipid metabolism and arteriosclerosis pathways (see **Fig. 7**). Among the 235 screened targets, approximately 70 are implicated in these pathways, including AKT, TP53, and SRC. Prior studies have established a connection between *Orthosiphon aristatus* and potential treatments for hypertension, underscoring the importance of these targets in regulating lipid metabolism and arteriosclerotic processes. This integrated analysis provides deep insights into the potential mechanisms of action of active components from *Orthosiphon aristatus* in managing hypertension through the modulation of pertinent biological pathways. (MATSUBARA et al., 1999; Ohashi, Bohgaki, & Shibuya, 2000; Ohashi, Bohgaki, Matsubara, et al., 2000).

Molecular docking tests using AutoDock Vina were conducted with coordinates 38.986625, 19.948107, 39.935679, and a grid size 30x30x30. The five compounds showed the best binding affinities. Scutellarein (CID: 5281697) and aurantiamide acetate (CID: 124319) achieved the highest scores, at -8.0 kcal/mol, indicating a strong potential for binding to relevant protein targets. Scutellarein formed hydrogen bonds with ASP1833, HIS178, MET243, and ASN239, while aurantiamide acetate formed hydrogen bonds with ARG1744, ASN1842, and ARG174. Cryptotanshinone (CID: 160254) and baicalein (CID: 5281605) also showed promising results with scores of -7.8 kcal/mol and -7.7 kcal/mol, respectively, forming hydrogen bonds with residues GLN1718, HIS178, MET243, and ASN239. Rosmarinic acid (CID: 5281792), with a score of -7.0 kcal/mol, demonstrated significant interactions with various amino acid residues such as VAL172, GLU171, ARG175, GLU180, ASN1845, ALA1714, and LEU1715. These findings provide valuable insights into the potential of these compounds as therapy candidates in hypertension.

CONCLUSION

This study utilized computational systems pharmacology to investigate how active compounds from *Orthosiphon aristatus* interact with hypertension targets. Screening based on physicochemical properties and pharmacokinetic data identified 28 promising compounds. Analysis with PKCSM indicated favorable pharmacokinetic profiles, including good absorption and distribution. However, some compounds showed CYP2D6 inhibition. Toxicity analysis revealed low toxicity levels overall, except for p-Cymene. Protein-protein interaction analysis identified hypertension-related targets like TP53, AKT1, STAT3, and SRC. Compounds such as oroxylin A, 3-hydroxy-5,7,4-trimethoxyflavone, tanshinone IIA, eugenol, and rosmarinic acid demonstrated strong affinity with these targets, known for their blood pressure-lowering effects. KEGG pathway and GO function analyses highlighted *Orthosiphon aristatus* potential in treating hypertension, particularly in lipid pathways. Scutellarein and aurantiamide acetate showed the highest affinities with -8,0 kcal/mol. This research provides insights into *Orthosiphon aristatus* efficacy as a safe and effective antihypertensive agent.

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