Indonesian Journal of Pharmacy

VOL 35 (4) 2024: 712–722 | RESEARCH ARTICLE

Network Pharmacology and Molecular Mechanism of Traditional Indonesian Medicine in Hypertension Treatment

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Article Info

Submitted: 12-08-2023
Revised: 30-04-2024
Accepted: 16-05-2024

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ABSTRACT

Scientific herbal formulations are used clinically to treat hypertension, but their functional molecular mechanisms remain unclear. This study identified the molecular pathways of scientific herbal remedies in treating hypertension work. The identified compounds were then excluded by measuring oral bioavailability and drug similarity. The network was created using Cytoscape version 3.8, and the predicted target information was obtained from a number of databases, such as SwissTarget Prediction, STRING, Online Mendelian Inheritance in Man, and Kyoto Encyclopedia of Genes and Genomes (KEGG). The decoction's method for lowering hypertension was then clarified using an enrichment analysis. It was discovered that bioavailability and drug similarity metrics existed for 44 identified substances. The results of pathway analysis using KEGG revealed that the potential targets were correlated with the antihypertensive mechanism of herbal medicine such as the HIF-1, relaxin, PI3K, and MAPK signaling pathway. Scientific herbal formulas' pressure-lowering mechanisms include those related to vascular endothelium and atherosclerosis, which involve several signaling pathways such as HIF-1, relaxin, PI3K, and MAPK.

Keywords: hypertension, jamu, molecular mechanism, network pharmacology

INTRODUCTION

The prevalence of hypertension is predicted to increase; about 29% of adults worldwide will be affected by the disease in 2025 (WHO, 2021). The disease poses a public health threat as it can lead to complications such as stroke, coronary artery disease, and renal failure (Tocci *et al*., 2020). The biodiversity in Indonesia is particularly abundant in medicinal plants. For ages, Indonesian people have used the traditional medicine known as jamu to prevent illness and treat it. Herbal medicine remains popular in both rural and urban areas, even though modern medicine is becoming more widely used and becoming the main treatment option (Elfahmi *et al*., 2014). The most common kind of traditional medicine, like jamu, is a steeping powder or liquid that comprises various medicinal plants, each of which contains various components. In general, the way of making herbal medicine refers to recipes inherited from ancestors that are composed of one or more types of plants with other neutral additives. There are various kinds of components and active ingredients mixed in herbal medicines. The action mechanism of traditional medicinal herbs is different from ordinary drugs. For example, the efficacy of Kampo, a traditional medicine from Japan, is based on the interaction of many compounds and many targets (Sawada *et al*., 2018).

In 2013, Basic Health Research showed that 30.4% of the public used traditional health services and 49.0% of it used herbal ingredients (Riskesdas, 2013). *Zingiber officinale* (50.36%), *Kaempferia galanga* (48%), *Curcuma xanthorriza* (39.5%), *Phyllanthus niruri* (13.93%), and *Morinda citrifolia* (11.17%) are among the commonly used medicinal plants for herbal preparations. To ensure the availability of safe, efficacious, and quality herbal medicine, the government is taking steps and making efforts to strengthen scientific information and data about herbal medicine, especially herbal formulas. The Indonesian government is carrying out a scientifically based herbal medicine development program through service-based research, which includes transforming medicinal plants into scientific herbal medicine. One of the

stages involves the selection of potential herbal formulas for alternative or complementary therapies (Riskesdas, 2010). For example, research conducted by Penelitian dan Pengembangan Tanaman Obat dan Obat Tradisional (B2P2TOOT) Indonesia resulted in a scientific jamu consisting of six plants, such as *Centella asiatica*, *C. xanthorrhiza*, *Curcuma domestica*, *Orthosiphon aristatus*, and *P. niruri* (B2P2TOOT, 2017). This jamu has been used to treat patients with hypertension in Hortus Medicus Clinic in Tawangmangu, Solo, Indonesia. *C. asiatica* exhibits hypotensive effect with the mechanism like ACE inhibitor (Mohebbati *et al*., 2020). *C. xanthorrhiza* and *C. domestica* contain secondary metabolite called curcumin. *Curcumin* can inhibit the occurrence platelet aggregation, which is triggered by the presence collagen, adrenaline, and arachidonic acid. Curcumin is a powerful antioxidant capable of suppressing the number of free radicals cause kidney damage systemic hypertension occurs. Quercetin content of *Orthosiphon aristatus* can lower blood pressure preventing aggregation platelets and thrombus. *Apium graveolens* leaves have diuretic activity effect on decreasing rate sodium and potassium in the blood. Decoction of *Phyllanthus niruri* can relax smooth muscle blood vessels and decrease myocardial contraction so it can lower the blood pressure (Triyono *et al*., 2018).

However, the molecular mechanism pathways of this herbal medicine to treat hypertension remains unclear. It is crucial to prove the molecular activity of the active compounds contained in each plant. This can be resolved by applying network pharmacology. Network pharmacology is a computer technique to explore the interaction of drugs and the targets and disease signaling pathways, design drug-based experiments and therapeutic targets for multigene-dependent diseases, and identify disease-causing genes (Jia-Ming *et al*., 2019). Thus, in this study, we used it to investigate the molecular mechanism pathways of the existed jamu's ability to treat hypertension. This research was prospective medication and hypertension-related targets, and jamu's compounds were computationally tested for oral bioavailability (OB) and drug similarity (DL).

MATERIALS AND METHODS

Online Mendelian Inheritance in Man (OMIM), Uniprot, SwissADME, Molsoft, Swiss Target Prediction, Cytoscape, a database for annotation and visualization, and Integrated Discovery (DAVID). The data of compounds contained in jamu was collected from KNApSAcK and IJAH Analytics. The OB and DL of each compound was investigated using SWISSADME and Molsoft. Subsequently, the proteins related to hypertension were collected from OMIM and Uniprot. Those proteins related to the active compounds in jamu were predicted using SWISS Target Prediction. Further, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) were analyzed using DAVIS to observe the biological pathways of jamu in reducing blood pressure. The network of jamu, plants, active compounds, and proteins was visualized using Cytoscape (Figure 1).

Preparation of plant materials

Hypertension herbal formula consists of *Apium graveolens* L., *O. aristatus (Thunb.)*, *C.asiatica (L.)*, *C. xanthorriza*, *P. niruri*, *and C. domestica*. The compounds contained in each plant were obtained from KNApSAcK (http://www.knapsackfamily.com/KNApSAcK/) and IJAH Analytics databases (http://ijah.apps.cs.ipb.ac.id/#/home).

Screening for oral bioavailability (OB), drug-likeness (DL), and creation of a compound-target network

Predicted target interactions with compounds are stored in the SwissTargetPrediction database (http: //www.swisstargetprediction.ch/) that was created with the Cytoscape program version 3.8, based on relationships between chemical similarity and visual interaction networks of complex targets (Gfeller *et al*., 2014; Shannon *et al*., 2003). Filtered bioactive substances were those with OB 55% and DL >0. The Uniprot database (http://www.uniprot.org/) contains all gene names.

Target protein data compounds compilation

The protein data as the binding target of the compound can be identified through the Swiss target prediction database. The data input to this database are compounds in SMILES format, and the species used is *Homo sapiens*. The results of the Swiss target prediction are then downloaded in Excel format.

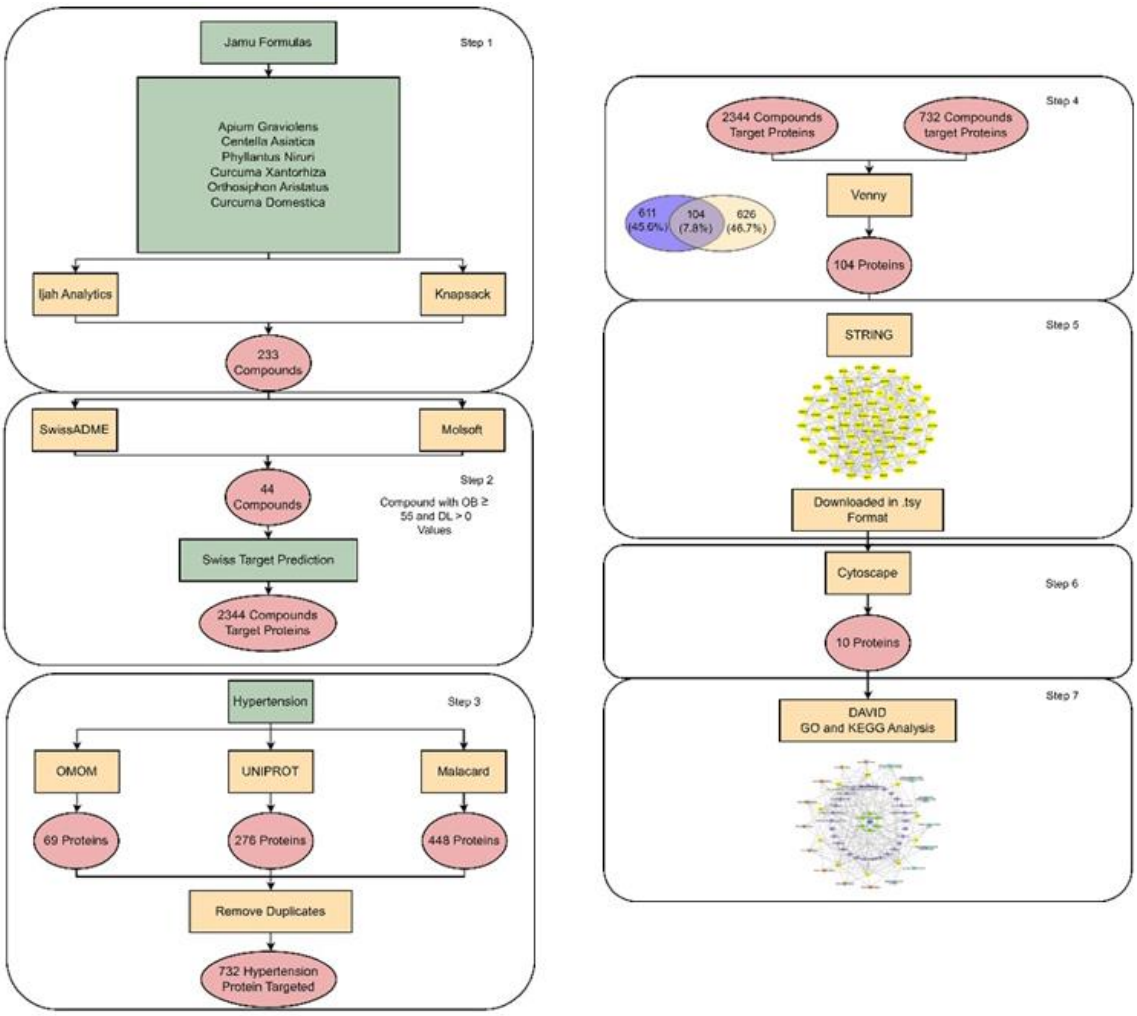

Figure 1. Network flowchart of jamu, plants, active compounds, and proteins visualized using Cytoscape

Establishing a gene network for hypertension

Using the keywords "Hypertension and genes associated with *Homo sapiens*" and excluding other species, you can find genes related to hypertension and cardiovascular disease online at Mendelian Inheritance in Man (OMIM) (https://omim.org/), Uniprot database (http://www.uniprot.org/), and the MalaCards database on human diseases. OMIM is a comprehensive research resource on human genes and inherited diseases. The well-known GeneCards human genetic database's architecture and depth served as the foundation for MalaCards, an integrated database of human diseases and associated annotations. All of these databases are free, comprehensive online tools that can provide a fairly comprehensive overview of research findings. We then constructed target genes and protein-protein interaction networks (PPIs) using the identified genes for hypertension or cardiovascular disease.

Networks of protein-protein interactions (PPI) construction

The investigation of protein-protein interactions (PPI) was done with STRING 11.0 (https://string-db.org/). Following systematic co-expression analysis, identification of common selection signals across the genome, and automated text mining of the scientific literature, databases are developed and generated (Szklarczyk *et al*., 2019). For network analysis and data visualization, this was loaded into Cytoscape version 3.8 via STRINGApp (Doncheva *et al*., 2019); more trust in the interaction is indicated by a confidence value of 0.7.

Table I. Active compounds of scientific herbal formula with OB (oral bioavailability) and DL (drug-likeness) paraments.

Species	Compound name	OB (%)	DL
Apium Graveolens	(-)-Falcarinol	55	0.29
Apium graveolens	5-Methoxy-8-O-beta-D-glucosyloxy-psoralen	55	0.29
Apium graveolens	Apigenin	55	0.39
Apium graveolens	Celephthalide A	55	0.18
Apium graveolens	Celereoside	55	0.4
Apium graveolens	Chrysoeriol	55	0.3
Apium graveolens	Lunularic acid	56	0.31
A. graveolens	Luteolin	55	0.38
O.aristatus	Scutellarein tetramethyl ether	55	0.37
O. aristatus	Sinensetin	55	0.29
O. aristatus	2-(3,4- dimethoxyphenyl)-5-hydroxy-6,7-dimethoxy-4H-1-benzopyran-4-one	55	0.4
O.aristatus	5-hydroxy-6,7,3',4'-tetramethoxyflavone	55	0.4
O.aristatus	Eupatorin	55	0.46
O.aristatus	Scutellarein 5,6,7,4'-tetramethyl ether	55	0.37
Phyllanthus niruri	Quercetin	55	0.52
Phyllanthus niruri	Beta-glucogallin	55	0.81
Phyllanthus niruri	Beta-sitosterol	55	0.78
Phyllanthus niruri	Eriodictin	55	1.08
Phyllanthus niruri	Glucogallin	55	0.81
Phyllanthus niruri	Hypophyllanthin	55	0.81
Phyllanthus niruri	Kaempferol 4'-rhamnoside	55	0.57
Phyllanthus niruri	Lintetralin	55	0.37
Phyllanthus niruri	Nirtetralin	55	0.84
Centella asiatica	2-Alpha-hydroxyursolic acid	56	0.6
Centella asiatica	3-Epimaslinic acid	56	0.55
Centella asiatica	3-O-cis-caffeoylquercetin	55	0.65
Centella asiatica	3-O-cis-p- coumaroylkaempferol	55	0.67
Centella asiatica	Asiatic acid	56	0.77
Centella asiatica	Isothankunic acid	56	0.91
Centella asiatica	Kaempferol	55	0.67
Centella asiatica	Labiatenic acid	56	0.37
Centella asiatica	Madecassic acid	56	0.76
Centella asiatica	Pomolic acid	56	0.32
Centella asiatica	Ursolic acid	85	0.84
Curcuma domestica	1,5-dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one	55	0.36
Curcuma domestica	1,7-bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol	55	0.04
Curcuma domestica	3'-demethoxycyclocurcumin	56	0.54
Curcuma domestica	Camphor	55	0.11
Curcuma domestica	Xanthorrhizol	55	0.52

Table I. Continued

Species	Compound name	OB (%)	DL
Curcuma domestica	Tyrosine	55	0.06
Curcuma domestica	Glutamic acid	56	0.24
Curcuma domestica	Citric acid	56	0.52
Curcuma domestica	Acetic acid	85	0.55
Curcuma domestica	Uridine	55	1.07

Note: **OB (%):** Oral bioavailability (OB) refers to the percentage of the drug that enters the bloodstream when administered orally. A higher OB value indicates better absorption and availability in the body. Compounds with OB ≥55% are considered to have good bioavailability.

DL (Drug-Likeness): Drug-likeness (DL) is a parameter that measures the similarity of a compound to commercially available drugs. Compounds with DL values >0 are considered more likely to have drug-like properties, while negative or zero DL values indicate low similarity.

Network of protein interactions examined topologically

To assess the nodes in a network, properties such as connection degree (k), betweenness centrality (BC), and closeness centrality (CC) were used. k and BC are particularly important parameters in network theory (Raman, 2010). Degree (k), the most essential characteristic of a node in a network, is defined as the number of consecutive connections or the number of interactions that connect proteins to other nodes nearby. To determine how frequently a node appears on the shortest path between other nodes, BC is the fraction of the shortest paths that pass through each node. The length of each geodesic curve leading or terminating at a network vertex is used to determine the shortest path. High BC nodes significantly affect the network's flow of information. As a global attribute, BC is crucial as a useful metric for identifying network bottlenecks.

Signaling Pathway Analysis

The DAVID database (version 6.8; https://david.ncifcrf.gov) contains all possible targets. For a large number of genes or proteins, DAVID offers a systematic and thorough study of biological activities, such as biological processes, cellular components (CCs), molecular functions, and signaling pathways. There are options for annotations. In the KEGG analysis, the link between passes and goals is stronger the lower the P-value. There are more objectives on the road the higher the number. A P-value cutoff of 0.01 was considered statistically significant.

RESULTS AND DISCUSSIONS

Screening active compounds and related targets

The active compounds obtained from the KNApSAcK and IJAH Analytics databases after removing duplicates were 223 compounds. *Apiumn graveolens* contained 59 compounds, *Centella asiatica* 28 compounds, *Phyllanthus niruri* 24 compounds, *Curcuma xanthorrhiza* 54 compounds, *Orthosiphon aristatus* 18 compounds and *C. domestica* 39 compounds.

Drug target network construction, drug-likeness (DL), and oral bioavailability (OB) screening

High oral bioavailability is a crucial factor to consider while developing new medications. Poor oral bioavailability can lead to unequal exposure to the active ingredient, particularly if the mechanisms that limit the active ingredient are weakened in some people. In terms of bioavailability, drug-likeness evaluates qualitatively the likelihood that a molecule will be turned into an oral medication. Structure or physicochemical analyses of developing compounds regarded to be oral drug candidates allowed for the determination of a compound's drug-likeness (Daina *et al*., 2017). Compounds that met the requirements for OB and DL values were 44 compounds of which 8 compounds were obtained from *Apium graveolens*, 6 compounds from *Orthosiphon aristatus*, 9 compounds from *Phyllanthus niruri*, 11 compounds from *Centella asiatica,* 5 compounds from *Curcuma xanthorrhiza* and 5 compounds from *C. domestica* (Table I).

Collection of Target Protein Data Compounds

The results of protein data collection carried out on the Swiss target prediction database obtained as many as 2341 proteins from uniport and OMIM that are targets of the compound herbal formula. After removing duplicates, the protein target compound obtained 715 proteins.

Hypertension protein data search

There were 793 proteins obtained from the 3 databases, of which 69 were obtained from the OMIM database, 276 from Uniprot, and 448 from the Malacard database. After removing duplicates, the protein obtained 730 proteins.

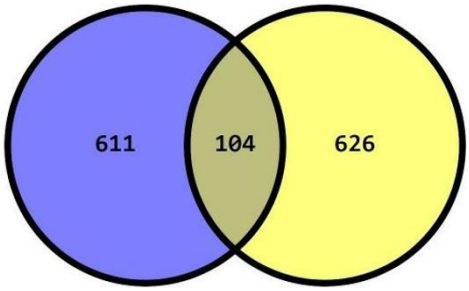

Figure 2. Venn diagram. The blue color indicates the target protein of the compound, and the yellow color indicates the hypertension protein in Indonesian Traditional Medicine for Hypertention.

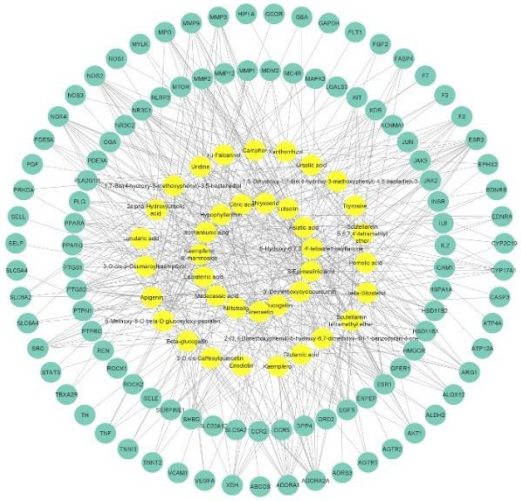

Figure 3. Visualization of the network between the compound and the target protein. The yellow color indicates the compound from herbal medicine, and the green color indicates the target protein.

Search for proteins related to diseases and compounds

In Venny's database, there were 104 proteins related to hypertension and compounds, seen in the Venn diagram slices (Figure 2 and 3).

Protein-protein interaction networks (PPI) construction

The STRING v.11 PPI network had the species set to "*Homo sapiens*," the maximum confidence as the minimal interaction threshold, and the highest confidence as 0.9. The default values for the remaining parameters were used. The postlaunch PPI network will consist of 78 nodes and 219 edges (Figure 4).

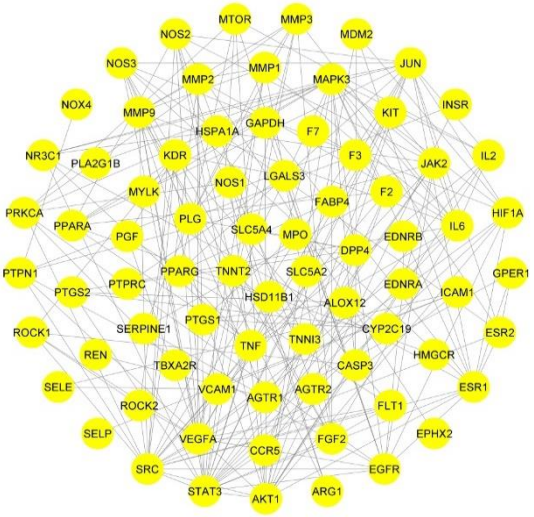

Figure 4. Protein-protein interaction (PPI) network of formula herbal for hypertension visualization in Indonesian Traditional Medicine for Hypertention.

Network topology analysis

Degree value indicates the amount of protein that interacts with other proteins. a protein with a high degree value indicates that the protein is a central protein or a protein that has the greatest role in protein regulation. By counting how many shortest routes travel through a node, BC calculates the number of routes. The distance between two nodes is the shortest path. The importance of a node increases with the shortest paths through it. The 10 proteins that have the highest degree and BC values are STAT3, SRC, MAPK3, VEGFA, AKT1, JUN, EGFR, IL6, JAK2, and NOS2 proteins (Table II).

Table II. Results of network topology analysis based on degree and betweenness centrality

Protein	*Degree centrality*	*Betweenness centrality*
STAT3	24	0.226337985
SRC	21	0.155147353
MAPK3	20	0.129502592
VEGFA	18	0.062361448
AKT1	17	0.128746474
JUN	17	0.078907935
EGFR	13	0.072994259
IL6	13	0.04861026
JAK2	11	0.057091371
NOS2	9	0.047495398

According to the network topology analysis, there were 10 significant proteins related to hypertension. By using Cytoscape, the proteins were arranged considering the degree and BC value. This finding is in line with the previous study. Setiani *et al*. (2023) found that MAPK3 is the significant protein related to hypertension that is the regulatory center of blood pressure. It has the potential of being the hypertension biomarker (Setiani, Saputri, *et al*., 2023).

Kyoto Encyclopedia of Genes and Genomes (KEGG)

Network visualization linking proteins, chemicals, biological processes, and KEGG signaling pathways is used to make it easier to trace each protein's biological processes and KEGG signaling pathways (Suppl, A1).

Cardiovascular disease (CVD), the main cause of death worldwide and a complicated disease influenced by complex genetic and environmental interactions, is at high risk for developing hypertension. In Indonesia, jamu is frequently used to treat various illnesses, such as hypertension, diabetes, and diarrhea. The herbal formula that consists of *Apium graveolens*, *Centella asiatica*, *Curcuma xanthorriza*, *Curcuma domestica*, *Phyllanthus niruri*, and *Orthosiphon aristatus* has been shown as an antihypertensive agent. This formula combination has a synergistic effect between each herbal. In this study, we initially used network pharmacology analysis to identify the main compounds, target proteins, and pathways of Indonesian scientific herbs against hypertension. Based on a systematic network perspective, a network pharmacology approach elucidates the potential mechanisms of herbal prescriptions for hypertension. It was discovered that these prescriptions successfully reduced blood pressure elevation in animal experiments, decreased RAAS activation in metabolic syndrome, and demonstrated their ability to prevent and normalize serum NO levels. The oral bioavailability and drug resemblance investigations resulted in 44 main compounds contained in this herbal formula. By pairing 44 active compounds with the associated 104 possible targets (Suppl, A1), we were able to create a connection target network. We created disease-compound-target protein networks to show the intricate interaction between the active compounds, shared targets, and route. One of the primary components of *Centella asiatica*, asiatic acid, has the ability to stop RAAS activation in rats with metabolic syndrome (Maneesai *et al*., 2017). High levels of asiatic acid help to normalize blood pressure and serum NO levels (Raman, 2010). Many studies have demonstrated that eNOS is crucial for preserving cardiovascular homeostasis and vascular function. Asiatic acid is a triterpenoid compound derived from *Centella asiatica*. Asiatic acid has antioxidative and anti-inflammatory properties. It also lowers blood pressure and improves vascular function by restoring endothelial nitric oxide synthase (eNOS), which is crucial for preserving cardiovascular homeostasis and vascular function and p47phox expression in L-NAME hypertensive rats (Bunaim *et al*., 2021). Endogenous NO suppresses vascular $p47^{phox}$ protein expression and superoxide production, which contribute to the source of vascular oxidative stress that initiates vascular inflammation and dysfunction (Bunbupha *et al*., 2014). Angiogenesis, vasodilation, and NO production are all controlled by eNOS, which also controls inflammatory processes. Endothelial dysfunction in hypertension has been linked to decrease NO bioavailability as one of the main causes (Bunaim *et al*., 2021). *Orthosiphon aristatus* contains quercetin and sinensetin, which have antioxidant properties, angiotensin-converting enzyme activity suppression, and improvements in endothelium-dependent and endothelium-independent function (Jie *et al*., 2021). Quercetin has been reported to block ACE in vitro, improve endothelium-dependent vasorelaxation of aortic segments, and lower systolic blood in rats, suggesting that these substances may be the source of the observed hypotension (Duarte *et al*., 2001; Larson *et al*., 2010). Meanwhile, sinensetin is assigned to antihypertension through its anti-inflammation, antidiuretic, and vasorelaxant properties. In addition, *Xanthorrhizol* in *Curcuma*

xanthorriza is able to relax smooth muscle cells in rat aorta probably due to its activity as a calcium antagonist, and that this effect is endothelium-independent (Campos *et al*., 2000).

We found that the hub targets of the herbal remedy for lowering blood pressure (Figure 4) were STAT3, SRC, MAPK3, VEGFA, AKT1, JUN, EGFR, IL6, JAK2, and NOS2 in the PPI network. In the endothelium, increased and persistent STAT3 phosphorylation has also been found. STAT3 has been linked to increased angiogenesis and proliferation. Endothelial barrier healing is the main component of the therapeutic approach for treating pulmonary arterial hypertension (Paulin *et al*., 2012). MAPK3 activates ERK1, which is involved in vasoconstriction and vascular smooth muscle cell growth, related to 1,7-bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol, 2-alpha-hydroxyursolic acid, and 3-epimaslinic acid. These compounds are included in curcuminoid, which has high antioxidant and anti-inflammatory properties (Rahmat *et al*., 2021). In addition, AKT1 plays a role of hypertension, and AKT1 hyperactivation triggers additional NO production that results in enlargement of blood vessel diameter and increased blood flow (Lee *et al*., 2014). It will have interactions with several compounds, such as scutellarein tetramethyl ether, 1,7-bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol, 2-(3,4-dimethoxyphenyl)-5-hydroxy,6,7-dimethoxy-4H-1-benzopyran-4-one, 5-hydroxy-6,7,3',4'-tetramethoxyflavone, apigenin, chrysoeriol, luteolin, and scutellarein 5,6,7,4'-tetramethyl ether. A previous study reported that apigenin plays a protective role in hypertension by decreasing oxidative stress, leading to normalizing blood pressure and restoring damaged kidneys in rats. It also controls the increase of blood pressure in rats with hypertension by increasing the bioavailability of nitric oxide (NO), reducing oxidative stress, and declining blood vessel damage (Xu *et al*., 2022).

The HIF-1 signaling route is a significant KEGG signaling circuit (Figure 5). Vascular endothelial growth factor (VEGF) expression has been demonstrated to be regulated by HIF-1. The HIF-1 signaling system has been linked to energy metabolism, angiogenesis, and the pathophysiology of ischemia and inflammation. The PI3K/HIF signaling pathway is crucial for cardiac and neurological protection (Zhang *et al*., 2018). Because relaxin is a peptide hormone with a mechanism for relaxing smooth muscles, the relaxin pathway has an association with blood pressure regulation. In lowering blood pressure, relaxin works by increasing NOS so that NO levels increase. Blood pressure homeostasis is maintained in part by NO produced by the vascular endothelium, and its lack can result in various cardiovascular disorders, such as hypertension and atherosclerosis. According to reports, NO controls adhesion molecule expression and activation and may have a role in the prevention and treatment of atherosclerosis, endothelial activation, and T-cell invasion. Many vasodilators can be reduced by nitric oxide synthase (NOS) inhibitors, which can also cause endothelium-dependent vasodilatory responses (Abman, 2009). Relaxin also has effects on endothelin inhibition, angiotensin II inhibition, VEGF production, and matrix metalloproteinase production that cause systemic and renal vasodilatation, increased arterial compliance, and other vascular changes.

A previous study by Febriyanti *et al*. (2014) showed that the administration of jamu in patients with hypertension could decline the blood pressure by about 12.67% and 2.33% for systolic and diastolic, respectively. This study is also in line with Hussaana *et al*. (2016) that the treatment with scientific hypertension jamu for 4 weeks had the same effect as captopril in reducing blood pressure. The combination of plants in jamu could give a synergetic effect to treat hypertension with a low side risk, especially for the liver and kidneys.

This study strengthens the jamu ability in lowering blood pressure. Each plant contains active compounds that play important roles in treating hypertension. Each compound has a specific interaction with protein related to hypertension. The combination of the compounds will have a synergetic effect in reducing blood pressure through a combination of relaxation of vascular smooth muscle and stimulation of muscarinic receptors, which mediate the release of relaxing factors (Adaramoye *et al*., 2009; Branković *et al*., 2010; Saputri *et al*., 2015).

CONCLUSION

This study investigated the active compounds in hypertension jamu and their interactions with the proteins related to hypertension using network pharmacology. Scientific herbal formulas' pressure-lowering mechanisms include those related to vascular endothelium and atherosclerosis, which involve several signaling pathways such as HIF-1, relaxin, PI3K, and MAPK. The target organs connected to the mechanism of blood pressure changes with the

usage of this scientific herb must be verified. This finding has proven the scientific rationale about jamu in treating hypertension.

ACKNOWLEDGMENTS

The Authors would like to thank the Faculty of Pharmacy and the Directorate of Research and Development, Universitas Indonesia for supporting and funding this study (PUTI Pascasarjana grant: NKB-032/UN2.RST/HKP.05.00/2023) and Jamu Saintific Clinic Hortus Medicus B2P2TOOT Tawangmangu for supporting antihypertensive jamu in this research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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