FJIF Vol.14, No.2, December 2024, Page: 99-109, pISSN: 2549-9068, eISSN: 2622-755X

FITOFARMAKA: Jurnal Ilmiah Farmasi

(FJIF)

https://fitofarmaka-fmipa.unpak.ac.id/

Research Article

Exploring the Potential Mechanism of 'X' Jamu Capsule for the Treatment of Hypertension Based on Network Pharmacology

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https://doi.org/10.33751/jf.v14i2.11

Article info:

Submitted : 6-11-2024
Accepted : 19-12-2024
Published : 30-12-2024

Published by:
Universitas Pakuan

ABSTRACT

Jamu is a traditional medicine derived from plants, animals, minerals, and galenic preparations, empirically used for treatment of various conditions, including hypertension. Hypertension is characterized by systolic blood pressure exceeding 140 mmHg and diastolic pressure over 90 mmHg. This study aims to elucidate the antihypertensive mechanism of Jamu capsule formulation which contain six plants i.e. *Apium graveolens*, *Orthosiphon aristatus*, *Imperata cylindrica*, *Phyllanthus niruri*, *Centella asiatica*, and *Curcuma xanthorrhiza*, using a network pharmacology approach to explore its multi-component, multi-target effects. A total of 187 compounds from the plants were identified using the Knapsack and IJAH Analytic databases. After filtering for drug-likeness (DL) and oral bioavailability (OB) criteria, 40 compounds were selected. Target proteins were identified using the SwissTargetPrediction, OMIM, and Uniprot databases, yielding 2,198 compound-related proteins and 338 hypertension-related proteins. Protein-protein interactions revealed 10 overlapping targets, analyzed using the Cytoscape software. Functional annotation via the Database for Annotation, Visualization, and Integrated Discovery (DAVID) identified the PI3K-Akt signaling pathway as the most critical mechanism, linked to increased nitric oxide (NO) production. This pathway promotes vascular relaxation and blood pressure regulation. Key proteins involved in this pathway include JAK2, MDM2, INSR, NOS3, and VEGFA, which are targeted by 10 active compounds derived from *O. aristatus*, *P. niruri*, *C. asiatica*, and *C. xanthorrhiza*. As conclusion, the antihypertensive mechanism of compounds in jamu capsules work by increasing nitric oxide levels, which relaxes blood vessels and affects blood pressure, thus this study provides insights into the molecular mechanisms of Jamu's antihypertensive effects, highlighting its potential as a natural therapeutic agent for hypertension.

Keywords: Hypertension; jamu; molecular; network pharmacology; proteins

INTRODUCTION

One significant issue is hypertension, which raises the risk of developing other illnesses like kidney failure, coronary heart disease, and stroke. The incidence of hypertension in Indonesia is 6–15%. Many people suffer from hypertension in rural areas that have not been reached by health services (Kemenkes.RI, 2019). Hypertension is when the heart pumps blood so forcefully that the blood pushes against the arteries. A person is diagnosed with hypertension if their systolic and diastolic blood pressures are greater than 140 and 90 mmHg, respectively (Alifariki, 2019). Synthetic chemical drugs generally use a single-component, single-target approach, which means that these drugs work on one receptor to treat one disease. The weakness of this single-component, single-target approach is in treating diseases with many factors. However, this weakness

can be overcome by involving several active compounds to treat disease by targeting several disease-causing proteins (Li & Zhang, 2013). Jamu is an example of a multi-component and multi-target drug that provides comprehensive treatment (Rosyadah et al., 2017). Jamu is a concoction or ingredient derived from plants, animals, minerals, galenic, or a mixture that has been used in medicine for generations and is based on experience (Rusnaeni et al., 2016). The utilization of traditional medicine, such as herbal medicine, is obtained empirically based on the heritage or experience of ancestors in Indonesia. Since ancient times, medicinal plants have been used to treat hypertension in single and combined forms (Abdul et al., 2021). Jamu antihypertensive contain *Apium graveolens* (Celery), *Orthosiphon aristatus* (Kumis kucing), *Imperatae Rhizoma* (Alang-Alang), *Phyllanthus niruri* L (Meniran), *Centella asiatica* L. (Pegagan), and *Curcuma xanthorrhiza* (Temulawak). The formula was chosen because it has been registered with Badan Pengawasan Obat dan Makanan (BPOM) and based on the number of sales of these products seen from several marketplaces in Indonesia and claimed empirically to be able to reduce high blood pressure in hypertensive patients.

Network pharmacology is a science based on network biology, systems biology, pharmacology, bioinformatics, and computational science. Network pharmacology is used to increase opportunities and make it easier to determine drug targets because network pharmacology can obtain data on compounds and their activities to cure diseases. The goal of network pharmacology is to find out how and where the inhibition and activation of disease targets by a compound occurs (Zhang, 2016).

The molecular mechanisms of herbal formulations used to treat hypertension were examined in a previous study that is related to jamu formulation in this study. After identifying the key compounds in the jamu formulation, those with insufficient oral bioavailability or drug similarity were excluded. A molecular network was constructed using Cytoscape, with target information gathered from databases like Swiss Target Prediction, STRING, OMIM, and KEGG. Enrichment analysis revealed that 44 compounds met the criteria. The antihypertensive effects of these herbal remedies are connected to pathways like HIF-1, Relaxin, PI3K, and MAPK, which are linked to vascular endothelium and atherosclerosis, according to KEGG pathway analysis (Setiani et al., 2024). Based on the explanation above, this study aimed to find out the antihypertensive mechanism of jamu capsule formulation using the Network Pharmacology method.

METHODS

Tools dan Materials

ASUS Laptop model P243OU with Intel Core i3-6100U specifications up to 2.30 GHz (P2430UJ-WO0063D) with 4GB of DDR4 SDRAM 2133MHz RAM. KNApSAcK, IJAH Analytics, OMIM (Online Mendelian Inheritance in Man), Uniprot, SwissADME, Molsoft, Swiss Target Prediction, Cytoscape, Database for Annotation, Visualization, and Integrated Discovery (DAVID). Protein data were obtained from the Online Mendelian Inheritance in Man (OMIM) and UniProt databases, and compound data were retrieved from the KNApSAcK and IJAH Analytics platforms.

Procedure

Collection of Compounds Data

The JAMU formula used consisted of six plants: *A. graveolens*, *O. aristatus*, *I. cylindrica*, *P. niruri*, *C. asiatica*, and *C. xanthorrhiza*. Compound data from each plant were collected using the KNApSAcK database (http://www.knapsackfamily.com/KNApSAcK_Family/) and IJAH analytics (http://ijah.apps.cs.ipb.ac.id/).

Compounds Screening

The OB value is obtained from the Swiss ADME database (http://www.swissadme.ch/) by inputting the compound in SMILES format and clicking run. The OB value will be displayed in the drug-likeness column, and the DL value is obtained from the Molsoft database (https://molsoft. com/) by inputting the compound in the SMILES format and calculating its properties, the DL value of the compound will be displayed. Compounds that meet the requirements with an OB value of ≥55% and a DL value of >0 are selected (Abdelrheem et al., 2021).

Collection of targets from compounds

The Swiss Target Prediction database (http://www.swisstargetprediction.ch/) was utilized to identify the target proteins of the compounds in Jamu. The species "Homo sapiens" was selected in the species column, the compounds were inputted in SMILES format, and "Predict Targets" was chosen.

The target proteins of the compounds were displayed in tabular form, which could be downloaded in Excel format.

Hypertension Protein Data Collection

The OMIM database (https://www.omim.org/) and UniProt (https://www.uniprot.org/) were used to determine the proteins associated with hypertension. The data obtained was saved in Excel format, and then protein duplicates were removed.

Search For Hypertension Protein, Which Is The Target of Compounds in Jamu Capsule

The Cytoscape application was run by inputting protein data related to hypertension and protein data that are the target of the compound. Input results were analyzed manually by looking at the protein linkages based on the edges of the proteins. Proteins that have two edges (1 edge is related to the compound, and the other edge is related to hypertension) are selected as proteins to be further analyzed.

Gene Ontology (GO) Analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG)

The process began with the creation of a quercetin stock solution at a concentration of 1000 µg/mL in a 50 mL volume. From this stock, a series of dilutions were prepared to achieve a range of lower concentrations: 10, 8, 6, 4, and 2 µg/mL, each in a 10 mL volume. For the spectrophotometric analysis, a specific mixture was prepared using each concentration. The procedure involved extracting 1 mL from each diluted solution and combining it with several reagents: 3 mL of ethanol, 2 mL of aluminum chloride ($AlCl_3$) at 10% concentration, and 2 mL of 1 molar sodium acetate (CH_3COONa). This mixture was then brought to a final volume of 10 mL in a volumetric flask by adding distilled water. Following preparation, the solutions were left to incubate for 30 minutes, allowing for complete reaction development. To determine the optimal wavelength for subsequent measurements, the two µg/mL solution was utilized. Its absorbance was measured across a spectrum ranging from 350 to 450 nanometers. This scan allowed for the identification of the wavelength at which maximum absorption occurred, which would serve as the reference point for future analyses (Hasan et al., 2023).

RESULTS AND DISCUSSION

Collection of Compounds Data

From the collection of compounds data, a total of 187 compounds were identified in plants used in Jamu formulation. *A. graveolens* contained 59 compounds, *O. aristatus* contained 18 compounds, *P. niruri* featured 24 compounds, *C. asiatica* contained 28 compounds, *C. xanthorrhiza* contained 54 compounds, and *I. cylindrica* contained 4 compounds (Figure 1).

Screening of Compounds Data

To ensure that a compound functions effectively as a drug, it is crucial to predict its oral bioavailability (OB) and drug-likeness (DL) values. Oral bioavailability refers to the proportion of a drug that reaches the systemic circulation and is available to interact with target tissues after oral administration (Rachmania et al., 2018). An OB value of ≥55% is considered indicative of good oral bioavailability, as it reflects the drug's efficiency in reaching the bloodstream in sufficient quantities (Martin, 2005). Drug-likeness (DL) analysis evaluates how similar a compound is to commercially available pharmaceuticals based on its chemical properties. Compounds with negative or zero DL values indicate that they lack the structural and chemical characteristics typical of drugs, which can affect their potential for therapeutic use. As a result, these compounds are excluded from further analysis, as they are less likely to exhibit desirable pharmacokinetic and pharmacodynamic properties (Abdelrheem et al., 2021). In this study, compounds from the Jamu formulation were screened, and 40 compounds were selected that met the necessary OB and DL criteria, as shown in Table 1. These included 9 compounds from *A. graveolens*, 6 from *O. aristatus*, 9 from *P. niruri*, eleven from *C. asiatica*, and 5 from *C. xanthorrhiza*. Meanwhile, *I. cylindrica* contained no compounds that met the OB and DL requirements (OB ≥55% and DL > 0).

Collection of Targets from Compounds

This process was carried out to trace the target proteins that connected with the compound in jamu as antihypertension. It was carried out on the Swiss Target Prediction database and obtained 2198 proteins with links to 40 compounds, which are the ingredients of jamu as antihypertension.

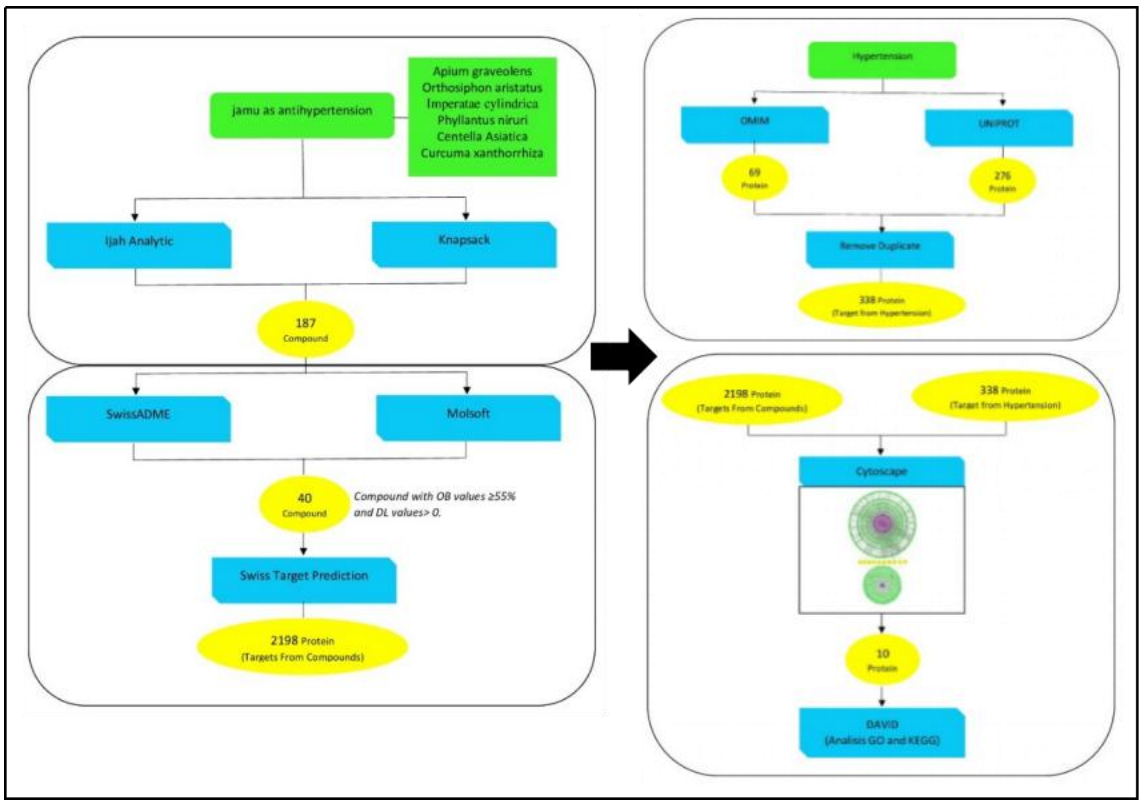

Figure 1. Workflow of the study.

Hypertension Protein Data Collection

As many as 276 proteins were obtained in the Uniprot database and 69 proteins in the OMIM database, then a duplicate was performed on both data sets to remove the same protein to obtain 338 proteins related to hypertension. This was done on these two databases to maximize the protein obtained because each database has a different novelty.

Search for the Hypertension Protein, which is the Target of the Compound

There are ten target proteins of compounds related to hypertension, namely NOS3, PPARG, PDE3A, AGTR1, NR3C2, JAK2, MDM2, GPER1, VEGFA, and INSR (Figure 2). This result can be seen from the proteins in the yellow nodes, which have edges towards compounds (purple nodes) and hypertension (blue nodes). At the same time, the green nodes are protein targets for each compound and disease.

Gene Ontology (GO) Analysis and KEGG

The GO analysis shows that the hypertension protein associated with the compound contained in jamu as antihypertension is involved in biological processes. Biological processes are processes that occur in the bodies of living organisms. In the GO analysis, sixty-five biological processes were obtained. Eleven of the sixty-five biological processes were identified based on the correlation of blood pressure reduction with assessment variables. These controls include gene expression, phosphatidylinositol 3-kinase, MAPK cascade, cell proliferation, vascular smooth muscle cell proliferation, nitric oxide biosynthesis, and blood pressure. A diagram representing the biological processes is used to display the GO analysis results, and Figure 3 shows the number of counts for each pathway. Meanwhile, the GO analysis that is not selected is data that, after being analyzed, can increase blood pressure or affect other diseases such as diabetes or cancer.

Seven pathways were identified by KEGG analysis: PI3K-Akt, cGMP-PKG, HIF-1, calcium, aldosterone-regulated sodium reabsorption, VEGF, and renin secretion. The results of this KEGG analysis are as a diagram between the paths and the number of counts of each pathway. The diagram can be seen in Figure 4.

Visualization of Networks Between Jamu-Plants-Compounds-Protein-Analysis GO and KEGG

The network visualization shows the relationship between plants, compounds, target proteins, GO analysis, and KEGG analysis. This step is taken to make it easier to trace the results obtained from each process carried out. Figure 5 shows a visualization of each process with information. The blue color indicates jamu as antihypertension, the purple color indicates the plant, the red color indicates the compound, the yellow color indicates the target protein, the green color indicates GO analysis, and the gray color indicates KEGG analysis.

Table 1. Compounds that Meet the Requirements of OB (*Oral Bioavailability*) and DL (*Druglikeness*) Values

Source	Compound	OB (%)	DL
Apium Graveolens	(-)-Falcarinol	55	0.29
	5-Methoxy-8-O-beta-D-glucosyloxy-psoralen	55	0.29
	Apigenin	55	0.39
	Celephthalide A	55	0.18
	Celereoside	55	0.4
	Chrysoeriol	55	0.3
	Lunularic acid	56	0.31
	Luteolin	55	0.38
	Scutellarein tetramethyl ether	55	0.37
	Sinensetin	55	0.29
Orthosiphon aristatus	2-(3,4-Dimethoxyphenyl)-5-hydroxy-6,7-dimethoxy-4H-1-benzopyran-4-one	55	0.4
	5-Hydroxy-6,7,3',4'-tetramethoxyflavone	55	0.4
	Eupatorin	55	0.46
	Scutellarein 5,6,7,4'-tetramethyl ether	55	0.37
	Quercetin	55	0.52
Phyllanthus niruri	Beta-glucogallin	55	0.81
	beta-Sitosterol	55	0.78
	Eriodictin	55	1.08
	Glucogallin	55	0.81
	Hypophyllanthin	55	0.81
	Kaempferol 4'-rhamnoside	55	0.57
	Lintetralin	55	0.37
	Nirtetralin	55	0.84
Centella asiatica	2alpha-Hydroxyursolic acid	56	0.6
	3-Epimaslinic acid	56	55
	3-O-cis-Caffeoylquercetin	55	0.65
	3-O-cis-p-Coumaroylkaempferol	55	0.67
	Asiatic acid	56	0.77
	Isothankunic acid	56	0.91
	Kaempferol	55	0.67
	Labiatenic acid	56	0.37
Curcuma xanthorrhiza	Madecassic acid	56	0.76
	Pomolic acid	56	0.32
	Ursolic acid	85	0.84
	1,5-Dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one	55	0.36
	1,7-Bis(4-hydroxy-3-methoxyphenyl)-3,5-heptanediol	55	0.04
	3'-Demethoxycyclocurcumin	56	0.54
	Camphor	55	0.11
	Xanthorrhizol	55	0.52

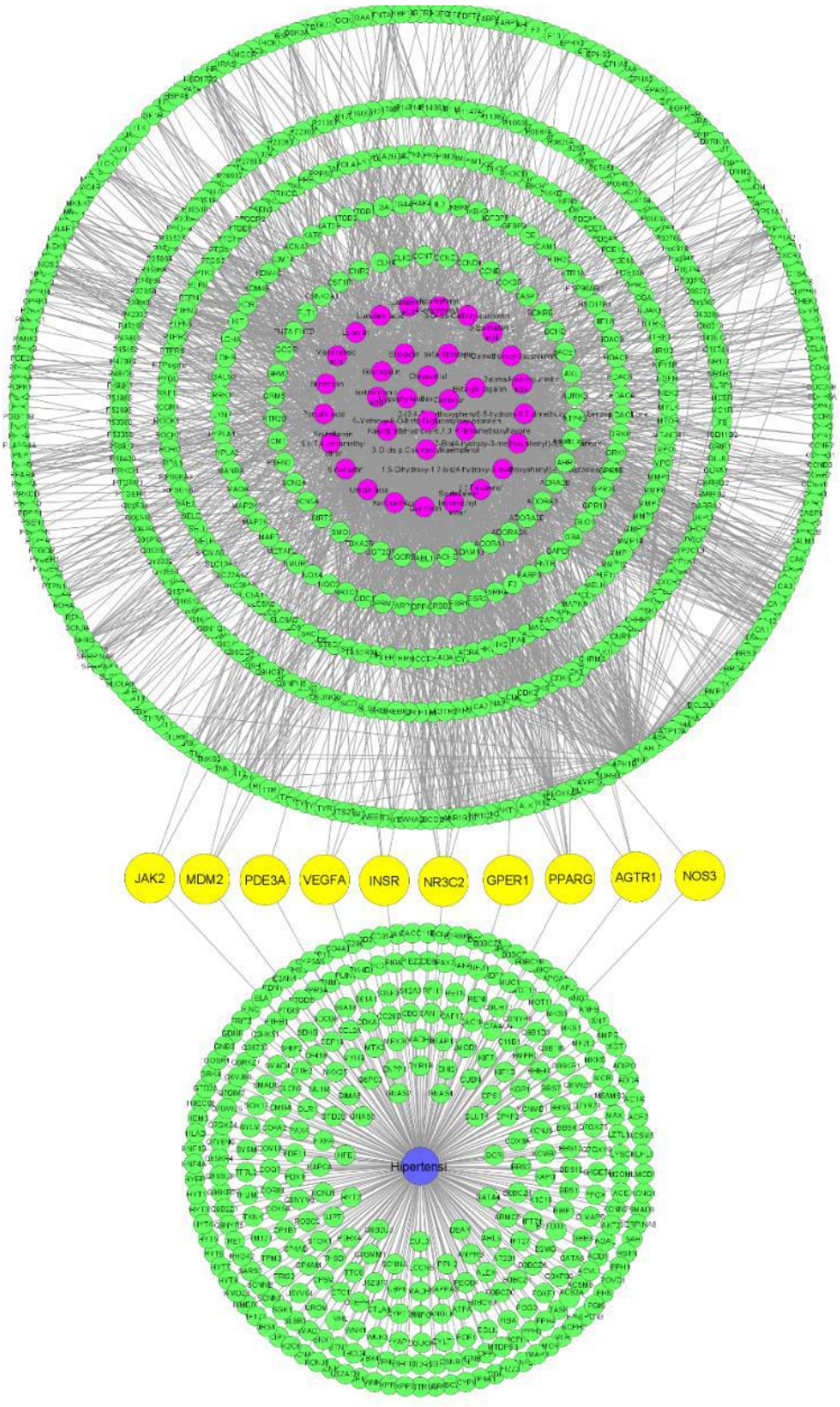

Figure 2. Visualization of hypertension protein which is the target of the compound

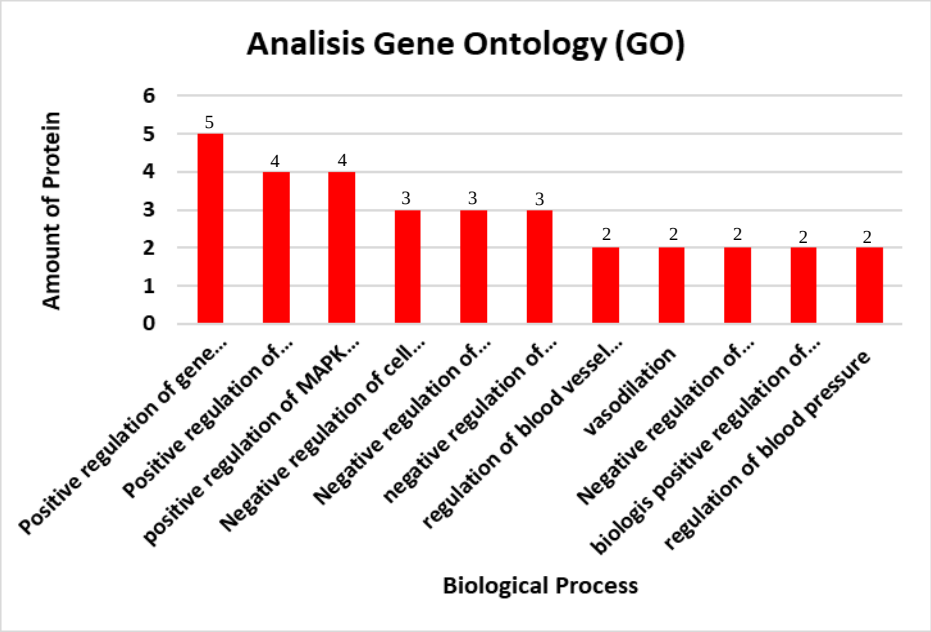

Figure 3. Biological Process in the Analysis of GO Jamu as Antihypertension

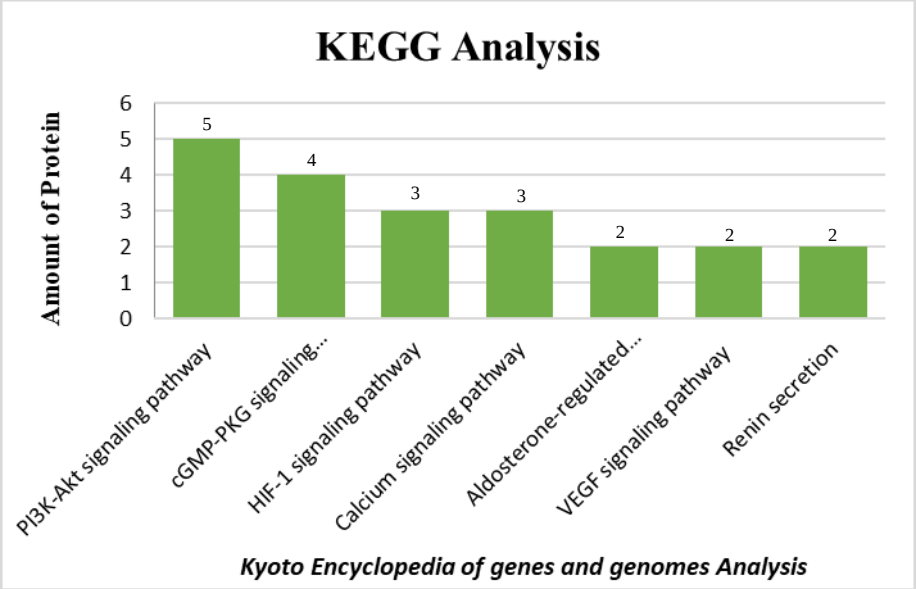

Figure 4. KEGG analysis of jamu capsule as antihypertension

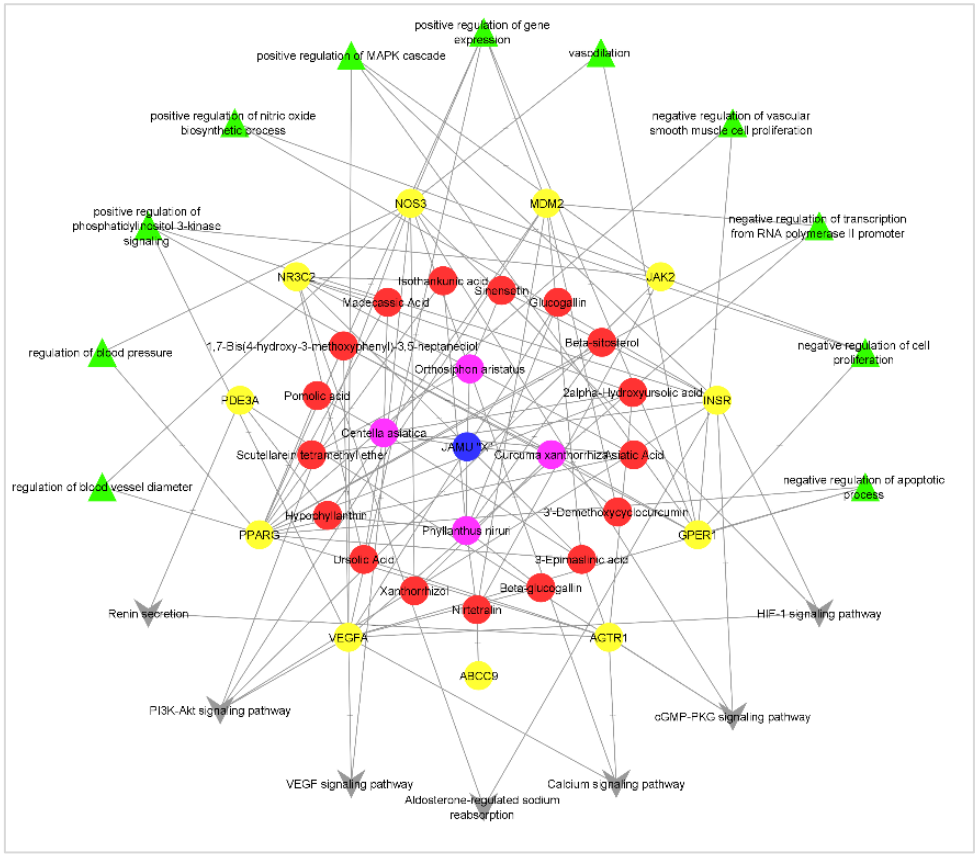

Figure 5. Visualization of Networks Between Jamu-Plants-Compounds-Protein-Analysis GO and KEGG

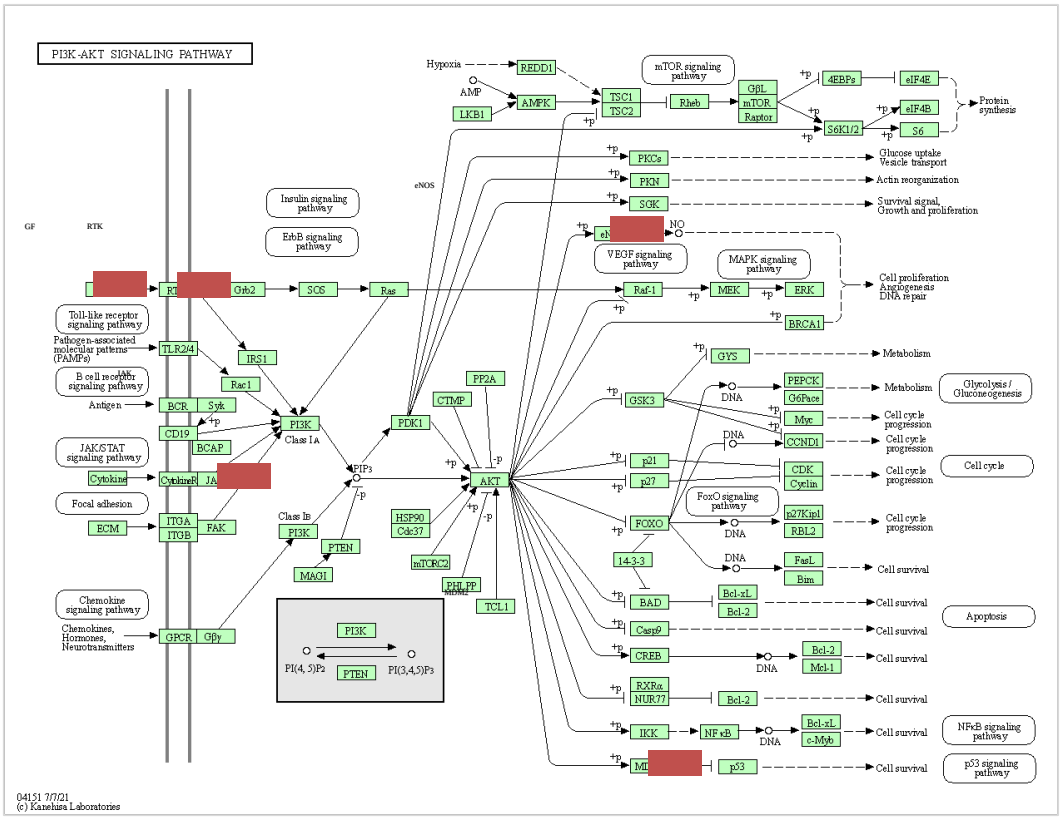

Figure 6. PI3K-Akt Signaling Pathway

Discussion

Hypertension affects a significant proportion of Indonesians, necessitating more diverse and accessible treatment options (Kemenkes RI, 2018). Herbal medicine has regained popularity due to people's increasing tendency to return to natural remedies, influenced by advancements in technology. Traditional medicine, particularly herbal remedies, is widely preferred by Indonesians due to its long history, accessibility, ease of preparation, and the perception of safety attributed to its natural ingredients (Biomedika & Adiyasa, 2021).

Hypertension has key factors, including angiotensin II, endothelin, and nitric oxide. Increased nitric oxide production can inhibit endothelin release so that angiotensin II production is reduced. This can lower blood pressure, which was initially high (Peng, 2020).

The *Centella asiatica* plant contains Asiatic acid, which has anti-inflammatory and antioxidant properties. Furthermore, it restores endothelial nitric oxide synthase (eNOS), which is essential for preserving cardiovascular homeostasis and blood vessel function, lowering blood pressure, and enhancing blood vessel function. In L-NAME hypertensive rats, it also increases p47phox expression (Bunaim et al., 2021). Quercetin and sinensetin, which are found in Orthosiphon aristatus, have antioxidant properties and inhibit the activity of enzymes that convert angiotensin. (Han Jie et al., 2021). The plant *Curcuma xanthorrhiza* contains xanthorrhizol. Due to its properties as a calcium antagonist, xanthorrhizol can relax rat aortic smooth muscle cells. This effect is not endothelium-dependent. (Campos et al., 2000). The primary ingredient in Apium graveolens, apigenin, has been demonstrated in a prior study to lower oxidative stress, normalize blood pressure, and restore kidney function in rats. Furthermore, by improving nitric oxide (NO) bioavailability, decreasing oxidative stress, and minimizing blood vessel damage, apigenin lowers hypertensive rats' elevated blood pressure (Xu et al., 2022).

Biological processes identified through Gene Ontology (GO) analysis suggest that compounds in *A. graveolens*, *O. aristatus*, *I. cylindrica*, *P. niruri*, *C. asiatica*, and *C. xanthorrhiza* have potential antihypertensive effects. The phosphatidylinositol 3-kinase (PI3K) pathway plays a key role in lowering blood pressure by enhancing inositol 3-kinase signaling, which positively regulates the PI3K cascade. This activation can stimulate endothelial nitric oxide synthase (eNOS), increasing nitric oxide (NO) availability, leading to vascular relaxation and blood pressure reduction (Wang et al., 2022). Additionally, the negative regulation of RNA polymerase II transcription inhibits superoxide production, which, when combined with nitric oxide, forms peroxynitrite, reducing NO levels and contributing to hypertension (Fauzan et al., 2020). Furthermore, the positive regulation of nitric oxide biosynthesis contributes to vessel relaxation, promoting vasodilation, which further reduces blood pressure (Fauzan et al., 2020).

In this formulation, compounds from *Centella asiatica*, *Orthosiphon aristatus*, and *Curcuma xanthorrhiza* are particularly influential in promoting vasodilation via the proteins NOS3 (endothelial nitric oxide synthase) and GPER1 (G-protein-coupled estrogen receptor 1). These proteins induce vasodilation by relaxing blood vessel smooth muscle, allowing blood to flow more freely, which in turn lowers blood pressure (Arief, 2022). Additionally, the negative regulation of cell proliferation by NOS3, GPER1, and JAK2 proteins plays a crucial role in preventing the excessive proliferation of vascular smooth muscle cells, which could otherwise lead to lumen stenosis and increased blood pressure (Mulyani et al., 2021).

To provide a more systematic approach, the key compounds in this formulation, particularly those from *O. aristatus*, *C. asiatica*, and *C. xanthorrhiza*, should be highlighted for their roles in controlling blood pressure. The oral bioavailability (OB) values of these compounds need to be assessed, with particular attention to those with OB values ≥55%, ensuring their effective absorption and bioavailability in the body for optimal antihypertensive effects. Further investigation into the mechanism of each compound's action will provide a clearer picture of their synergistic effects in managing hypertension. In addition to biological processes, looking at the signaling pathways traversed by the target protein through KEGG analysis is necessary. The pathway with the highest count value in the PI3K-Akt signaling pathway (Figure 6) is number 5, indicating that NOS3, INSR, MDM2, JAK2, and VEGFA are the five proteins involved.

The NOS3 protein plays a crucial role in blood vessel function because it produces nitric oxide (NO), which relaxes smooth muscle and promotes vasodilation. (Wang et al., 2021). INSR activates AKT, which in turn phosphorylates and activates eNOS, leading to increased production of nitric oxide (NO), a vasodilator. (Ridwan & Gotera, 2009). MDM2 is a protein that can stimulate the activity of protein kinase B (AKT). Reduced activation of AKT can inhibit the production of nitric oxide (NO), leading to impaired vasodilation.(Rahayu et al., 2017). JAK2 can cause vascular endothelial dysfunction, which reduces vasodilation due to inflammation resulting from the mobilization and interaction of white blood cells and platelets. (Tefferi et al., 2013). VEGFA mediates angiogenesis. In patients with hypertension, abnormal blood vessels are often present, making it necessary to stabilize vascular homeostasis through angiogenesis. (Zhao et al., 2020).

Figure 6 shows the signaling pathway between PI3K and Akt. The VEGFA protein is involved in the Growth Factor (GF), which binds to the Tyrosine Kinase Receptor (RTK), which is influenced by the INSR protein. This activation of the Insulin Receptor Substrate (IRS1) then stimulates PI3K. The protein JAK2 also affects PI3K excitation. In the cell membrane, PI3K subsequently catalyzes the synthesis of phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 then helps to trigger the act, which causes eNOS to generate NO.

CONCLUSION

According to the network pharmacology analysis, the antihypertensive herbs *A. graveolens*, *O. aristatus*, *I. cylindrica*, *P. niruri*, *C. asiatica*, and *C. xanthorrhiza* work by increasing nitric oxide levels, which relaxes blood vessels and affects blood pressure.

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