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Original Article

The mechanism of *Andrographis paniculata* (Burm.f.) Wall. ex Nees on upper respiratory infection by network pharmacology and molecular docking

[Mecanismo de *Andrographis paniculata* (Burm.f.) Wall. ex Nees en la infección de las vías respiratorias superiores mediante farmacología de red y acoplamiento molecular]

Truc-Ly Thi Duong[1], Thuy-Tien Thi Phan[2], Van-Ha Nguyen[3], Minh-Luan Nguyen[4], Dang-Khoa Nguyen[5]*

[1]Faculty of Traditional Medicine, Can Tho University of Medicine and Pharmacy, Can Tho 900000, Vietnam.
[2]Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, 11031, Taiwan.
[3]Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City 700000, Vietnam.
[4]Columbia College, Ho Chi Minh City 700000, Vietnam.
[5]Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Vietnam.
*E-mail: nguyendangkhoa@tdtu.edu.vn

Abstract

Context: In Chinese medicine, and Ayurvedic, *Andrographis paniculata* is traditionally employed as a remedy for colds and influenza, particularly to alleviate fever linked with infectious illnesses like upper respiratory infections (URIs).

Aims: To determine the potential anti-infective mechanisms of *A. paniculata* on upper respiratory infections through network pharmacology and docking modeling.

Methods: Initially, active chemical constituents of *A. paniculata* were identified using the Traditional Chinese Medicine Systems Pharmacology database. Subsequently, the target genes of these active ingredients were determined by the UniProtKB database, while target genes related to upper respiratory infections were identified through the GeneCards database. The compound-target network of AP was constructed by the Cytoscape. The protein-protein interaction network was generated using the STRING database. Further analysis was conducted through the DAVID database, integrating Gene Ontology and KEGG pathway enrichment analyses.

Results: Twenty-two active components of *A. paniculata* and highlighted key pathways such as the TNF signaling pathway, IL-17 signaling pathway, and human cytomegalovirus infection are potentially crucial for URIs treatment. Additionally, target genes of *A. paniculata,* including TNF, IL6, AKT1, TP53, CXCL8, CASP3, and PTGS2, were identified as significant in regulating these biological processes and pathways.

Conclusions: This study provides valuable insights into the mechanism of *A. paniculata* in treating URIs, laying the groundwork for further research in this area.

Keywords: *Andrographis paniculata*; molecular docking; network pharmacology; upper respiratory infections.

Resumen

Contexto: En la medicina china y ayurvédica, *Andrographis paniculata* se emplea tradicionalmente como remedio para los resfriados y la gripe, en particular para aliviar la fiebre asociada con enfermedades infecciosas como las infecciones de las vías respiratorias superiores (IVRS).

Objetivos: Determinar los posibles mecanismos antiinfecciosos de *A. paniculata* en las infecciones de las vías respiratorias superiores mediante farmacología de redes y acoplamiento molecular.

Métodos: Inicialmente, se identificaron los componentes químicos activos de *A. paniculata* utilizando la base de datos de farmacología de sistemas de la medicina tradicional china. Posteriormente, los genes diana de estos ingredientes activos se determinaron mediante la base de datos UniProtKB, mientras que los genes diana relacionados con las infecciones de las vías respiratorias superiores se identificaron mediante la base de datos GeneCards. La red compuesto-diana de AP se construyó mediante Cytoscape. La red de interacción proteína-proteína se generó utilizando la base de datos STRING. Se realizó un análisis adicional a través de la base de datos DAVID, integrando análisis de enriquecimiento de la vía KEGG y Gene Ontology.

Resultados: Veinte y dos componentes activos de *A. paniculata* y vías clave destacadas, como la vía de señalización del TNF, la vía de señalización de IL-17 y la infección por citomegalovirus humano, son potencialmente cruciales para el tratamiento de las infecciones de las vías respiratorias superiores. Además, se identificaron genes diana de *A. paniculata*, incluidos TNF, IL6, AKT1, TP53, CXCL8, CASP3 y PTGS2, como importantes en la regulación de estos procesos y vías biológicas.

Conclusiones: Este estudio proporciona información valiosa sobre el mecanismo de *A. paniculata* en el tratamiento de las infecciones de las vías respiratorias superiores, sentando las bases para futuras investigaciones en esta área.

Palabras Clave: acoplamiento molecular; *Andrographis paniculata*; farmacología de redes; infecciones de las vías respiratorias superiores.

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AUTHOR INFO
ORCID:
0009-0002-2063-5938 (TLTD)
0009-0004-0695-112X (VHN)
0009-0002-1569-2049 (MLN)
0000-0002-6681-7609 (DKN)

Abbreviations: GeneCards: The Human Gene Database; PPI: Protein-protein interaction; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; URIs: Upper respiratory infections; TCM: Traditional Chinese Medicine; TCMSP: Traditional Chinese Medicine Systems Pharmacology Database; OB: Oral bioavailability; DL: Drug-likeness; DAVID: Database for Annotation, Visualization, and Integrated Discovery; HCMV: Human cytomegalovirus; ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity.

INTRODUCTION

An upper respiratory tract infection (URIs), like the common cold, is a prevalent inflammatory condition characterized by mild symptoms affecting the nose, sinuses, throat, and voice box. It typically arises from viral infections, though occasionally, it may involve multiple causes. The symptoms of URIs depend on the individual's immune system and the specific pathogen involved. Common symptoms include sore throat, nasal congestion, sneezing, coughing, fatigue, low-grade fever, and headache. Inflammation of the mucous membranes can extend throughout the upper respiratory tract, affecting areas like the sinuses, throat, larynx, and nasal passages. Various viruses are known to cause these symptoms, including rhinoviruses, respiratory syncytial virus, influenza viruses, parainfluenza viruses, coronaviruses, and adenoviruses. Occasionally, other viruses like echoviruses, coxsackieviruses, Epstein-Barr virus, human metapneumovirus, and bocavirus may also be involved (Coerdt and Khachemoune, 2021; Worrall, 2011).

There has been growing interest in various biomedical fields regarding research on herbal and traditional medicine. Traditional herbal remedies have been consistently used to prevent and manage common cold symptoms, gaining recognition in scientific circles. Many medicinal plants offer relief from upper respiratory tract infections, alleviating symptoms like coughing, reducing fever, and clearing nasal congestion. These remedies predominantly rely on plant-derived compounds such as polyphenols, flavonoids, saponins, and alkaloids (Ciprandi and Tosca, 2021; Tran et al., 2023). One such remedy is *Andrographis paniculata* (Burm. f.) Nees (family *Acanthaceae*) refers to dried aerial parts of this species. It has traditionally been used for its properties in clearing heat and detoxification and alleviating fever linked with infectious illnesses like URIs. It contains bioactive compounds, including over 30 flavonoids, 55 diterpene lactones, 8 quininates, and 5 noriridoid compounds. Recently, pharmacological studies have shown that *A. paniculata* possesses antimicrobial, antiviral, cytotoxic, antiprotozoan, anti-inflammatory, and antioxidant properties, confirming its effectiveness in treating upper respiratory tract infections (Adiguna et al., 2021; Chandrasekaran et al., 2010; Chao and Lin, 2010).

Network pharmacology is becoming increasingly promising as it combines various technologies rooted in omics and systems biology. This approach is invaluable for gaining a comprehensive and systematic understanding of how multi-ingredient medicines work. When combined with Traditional Chinese Medicine (TCM), network pharmacology provides a robust method for investigating the underlying mechanisms of upper respiratory tract infections (URIs). It also offers a promising avenue for developing drugs to treat URIs (Chandran et al., 2017).

The study began with a systematic collection of information on the chemical constituents of *A. paniculata* from relevant Traditional Chinese Medicine (TCM) databases, then embarked on predicting the potential targets of these primary constituents and associating them with diseases linked to upper respiratory tract infections (URIs). Subsequently, enriched genes and pathways associated with these key targets were analyzed, with the aim of comprehending the pathways and mechanisms involved in treating URIs. Furthermore, several networks were constructed, including a constituent-target network, a protein-protein interaction network, and a constituent-target-pathway network. Then, the identified main targets were validated, using docking modeling. Finally, the ADMET profile of each key constituent was predicted.

MATERIAL AND METHODS

Mining of phytoconstituents and prediction of compound targets

The chemical constituents found in *A. paniculata* were sourced from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) using the keyword "Andrographis Herba". Compounds with an oral bioavailability (OB) of 30% or higher and a drug-likeness (DL) value of 0.18 or higher were considered favorable absorption and suitability for drug development, respectively. These criteria were employed to identify potentially active compounds in *A. paniculata*. The target genes of these effective compounds were obtained from the TCMSP databases (https://old.tcmsp-e.com/tcmsp.php).

Targets associated with upper respiratory infections (URIs) were searched for in the Human Gene Database (GeneCards) using keywords such as "Upper Respiratory Infection", specifying the species as *Homo sapiens* with a disease relevance score of 20 or higher. The gathered target genes were combined and any duplicates were eliminated. The Bioinformatics & Evolutionary Genomics platform

(https://bioinformatics.psb.ugent.be/webtools/Venn/) was employed to discover and visually represent the shared targets between the compounds found in *A. paniculata* and those related to URIs.

Based on these analyses, the active constituents were identified and target genes of *A. paniculata* matched with disease target genes of URIs, establishing compound-target interactions. To illustrate these relationships, Cytoscape 3.7.2 was used to construct a network diagram showing the connections between the active compounds of *A. paniculata* and the targets associated with URIs.

Gene expression and enrichment analysis

The identified overlapping targets were entered into String 11.0 (Search Tool for the Retrieval of Interacting Genes/Proteins, https://string-db.org/) to investigate interaction patterns among them, with the gene type specified as *Homo sapiens*. The resulting network was then visualized using Cytoscape 3.7.2. Network topology analysis involves considering the degree of a node, which indicates how many connections it has with other nodes. The degree values of nodes exceeding twice the median were identified as significant nodes, termed "core targets," indicating their importance in the network (Huang et al., 2024).

The DAVID database (Database for Annotation, Visualization, and Integrated Discovery, https://david.ncifcrf.gov/) is an online tool for gene annotation, classification, enrichment, and pathway analysis. This study employed DAVID to conduct Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. The significance threshold of $p<0.05$ for GO terms and $p<0.01$ for KEGG pathways were applied (An et al., 2021), and selected top entries resulting from these analyses were visualized for clarity.

The GO enrichment analysis examines the biological processes, molecular functions, and cellular components of the target proteins, whereas the KEGG enrichment analysis identifies potential biological pathways and functions linked to the targets.

Docking modeling analysis

Molecular docking was performed to confirm the interaction between the principal constituents of *A. paniculata*, reference drugs, and the key target genes. The 3D structures of key compounds and reference drugs were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and converted to PDB format using PyMol. The results were subsequently visualized using Discovery Studio software. Crystallographic structures of proteins corresponding to the major hub genes were retrieved from the Protein Data Bank (PDB) database (https://www.rcsb.org/). Docking pocket areas on the proteins were predicted using the DeepSite online tool, and unnecessary water molecules and ligands were removed using PyMol.

AutoDockTools was utilized to add hydrogen atoms, combine non-polar hydrogen atoms, calculate protein charges, and identify docking sites before docking. The key compounds were designated as ligands, and their torsions and roots were identified using AutoDockTools. Subsequently, both the primary hub target proteins and key compounds were converted to "pdbqt" format and entered into AutoDock Vina (https://vina.scripps.edu/) for docking modeling (Jiménez et al., 2017). The docking affinity scores lower than -6.0 kcal/mol suggest a robust binding interaction between the compounds and the target proteins.

ADMET profile of the key constituents

To evaluate the pharmacokinetic and toxicological characteristics of five key components extracted from *A. paniculata* and reference drugs, the admetSAR 3.0 web server (http://lmmd.ecust.edu.cn/admetsar3/) was utilized. This widely used online platform for ADMET predictions employs sophisticated machine-learning algorithms trained on extensive datasets of chemical compounds. These algorithms are capable of estimating various properties related to absorption, distribution, metabolism, excretion, and toxicity. The chemical structures of the five selected constituents were obtained in the SMILES format from PubChem. Each compound was submitted individually to the admetSAR 3.0 web interface for analysis. Human intestinal absorption, Caco-2 permeability, P-gp inhibition, plasma protein binding, hepatotoxicity, respiratory toxicity, acute oral toxicity, and other parameters were predicted (Thi Duong et al., 2024).

Data analysis

The TCMSP database was utilized to extract phytoconstituents from *A. paniculata*, while tools like SwissTargetPrediction were employed to identify target proteins, emphasizing those with high-confidence scores. URIs-related gene expression data was obtained from the Genecards database, with subsequent expression analysis to determine significant genes. GO and KEGG enrichment analysis, conducted via DAVID, illuminated crucial biological pathways. AutoDock Vina facilitated molecular docking simulations between key constituents, reference drugs, and protein targets, with PyMOL and BIOVIA Discovery Studio used to visualize binding affinity and interaction patterns. AdmetSAR 3.0 was employed to assess the ADMET profiles of key constituents, concentrat-

ing on desirable characteristics such as high bioavailability and low toxicity. Throughout the study, statistical analyses were applied, with significance thresholds of GO and KEGG set at $p<0.05$ and $p<0.01$, respectively.

RESULTS

Mining of phytoconstituents and target genes

The active constituents of *A. paniculata* were collected from the TCMSP database, resulting in 49 related constituents. Among them, 24 constituents met the criteria of having an oral bioavailability (OB) ≥30% and a drug-likeness (DL) ≥0.18 (Table 1). Through screening the GeneCards, 9601 genes URIs-related targets were identified, and 468 genes with relevance scores were found to have a score of ≥20. After identifying the gene associated with upper respiratory infection from Genecard, 22 compounds were obtained with genes related to the disease.

Using TCMSP databases, 183 targets were identified for these 22 active compounds of *A. paniculata* after removing duplicate targets.

Following a comparison with the 22 compound targets, a total of 18 shared targets were identified. These overlapping targets are illustrated in the Venn diagram (Fig. 1).

To gain further insights into the mechanism of *A. paniculata* in treating URIs, the compound-target network was constructed by using Cytoscape 3.7.2 software (Fig. 2).

Table 1. Information on 22 active compounds of *A. paniculata.*

Mol ID	Compound name	Molecular weight	Oral bioavailability (%)	Drug-likeness	Gene count
MOL000173	Wogonin	284.28	30.68	0.23	16
MOL002928	Oroxylin A	284.28	41.37	0.23	7
MOL008239	Quercetin tetramethyl(3',4',5,7) ether	358.37	31.57	0.41	5
MOL008228	Andrographin	328.34	37.57	0.33	5
MOL008206	Moslosooflavone	298.31	44.09	0.25	5
MOL008230	Andrographidine F_qt	374.37	77.13	0.45	4
MOL008222	Andrographidine B_qt	330.31	72.72	0.33	4
MOL002932	Panicolin	314.31	76.26	0.29	4
MOL008209	Deoxycamptothecine	332.38	50.01	0.77	3
MOL008213	14-Deoxy-12-methoxyandrographolide	364.53	70.29	0.36	2
MOL008216	Paniculide C	278.33	79.73	0.21	2
MOL008223	Andrographidine C	460.47	56.85	0.77	1
MOL008217	Paniculogenin	448.71	47.66	0.75	1
MOL008204	Mono-O-methylwightin	358.37	103.11	0.40	1
MOL008210	Deoxyelephantopin	344.39	105.32	0.40	1
MOL008232	(3Z,4S)-3-[2-[(1R,4as,5R,6R,8as)-6-Hydroxy-5,8a-dimethyl-2-methylene-5-methylol-decalin-1-yl]ethylidene]-4-hydroxy-tetrahydrofuran-2-one	350.5	46.96	0.36	1
MOL008234	Andrographolide-19-β-D-glucoside_qt	350.5	53.44	0.35	1
MOL008203	14-Deoxy-11-oxo-andrographolide	348.48	57.06	0.34	1
MOL008226	14-Deoxyandrographolide	334.5	56.3	0.31	1
MOL008219	3-[2-[(1R,4as,5R,8as)-5,8a-Dimethyl-2-methylene-5-methylol-decalin-1-yl]ethyl]-5H-furan-2-one	318.5	51.78	0.28	1
MOL008238	3-[2-[(1S,4ar,5S,8ar)-5,8a-Dimethyl-2-methylene-5-methylol-decalin-1-yl]ethyl]-5H-furan-2-one	318.5	63.54	0.28	1
MOL008215	Paniculide B	280.35	52.27	0.21	1

OB: Oral bioavailability; DL: Drug-likeness.

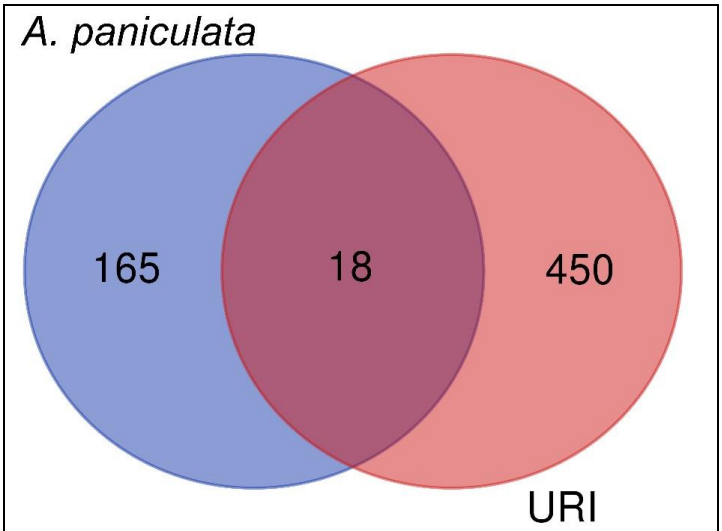

Figure 1. Venn diagram of the overlapping targets in *A. paniculata* and URIs.

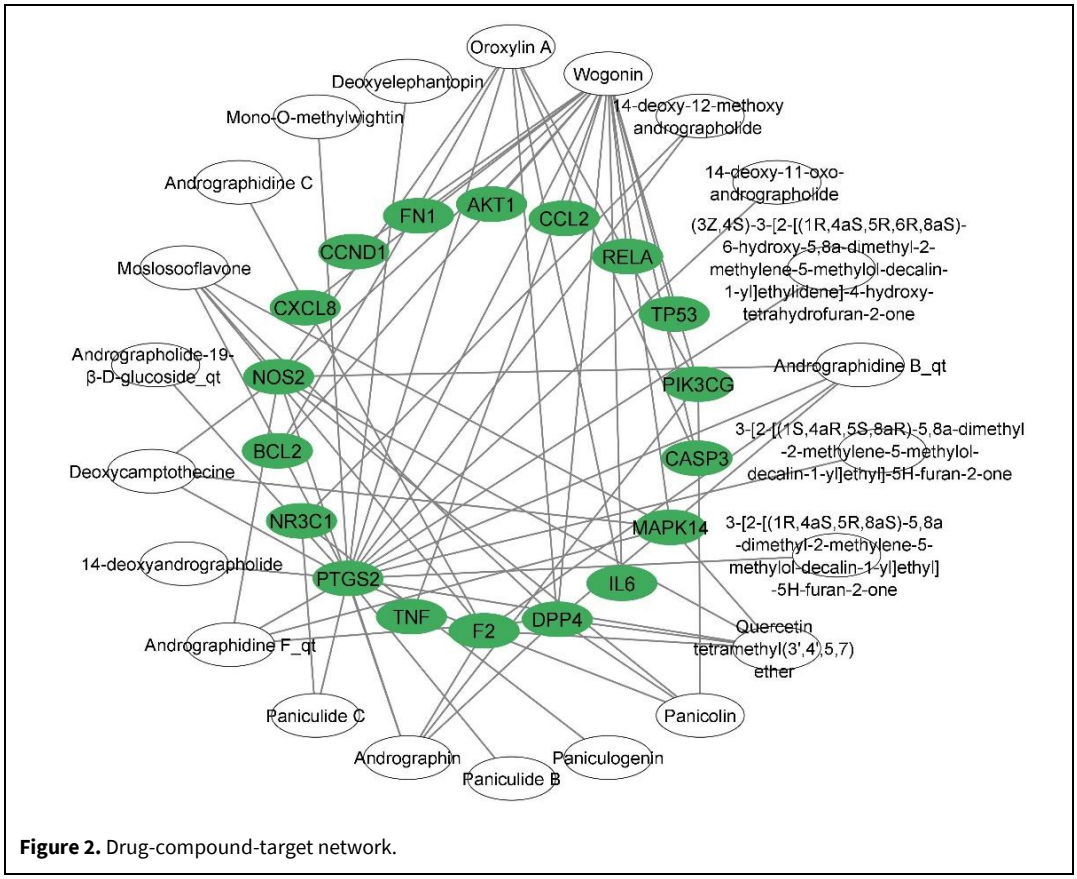

Figure 2. Drug-compound-target network.

This network visually represents the relationships between *A. paniculata*, its active compounds, and the target proteins involved in URIs.

Enrichment and network analysis

The protein-protein interaction (PPI) network derived from the 18 overlapping targets consisted of 120 nodes and 59 edges, as illustrated in Fig. 3.

Ten core targets were identified through a topological analysis by selecting those with a median degree value twice the average. These core targets are IL6, TNF, AKT1, TP53, CXCL8, CASP3, PTGS2, CCL2, BCL2, and FN1. A network diagram, displayed in Fig. 4, was created to represent the interactions among these core targets.

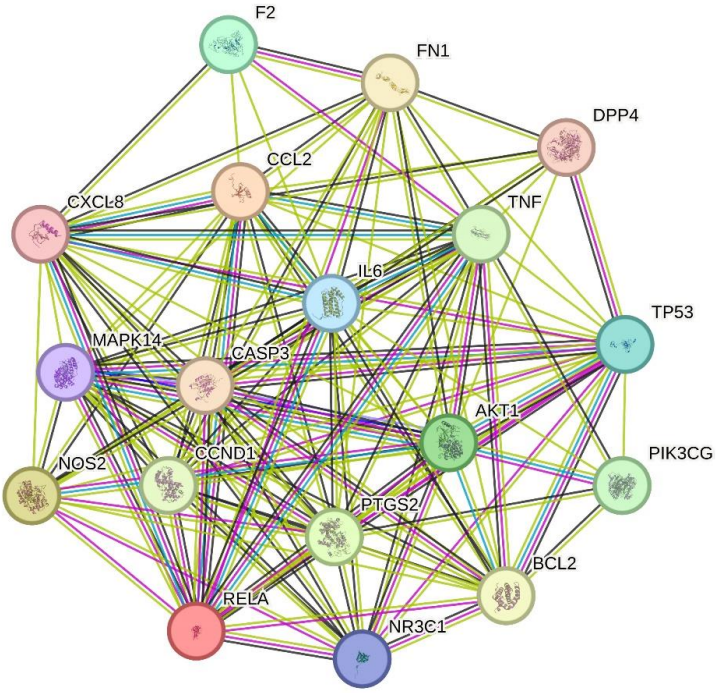

Figure 3. Protein-protein interaction network of 18 targets of *A. paniculata* against URIs. Edges represent protein–protein associations.

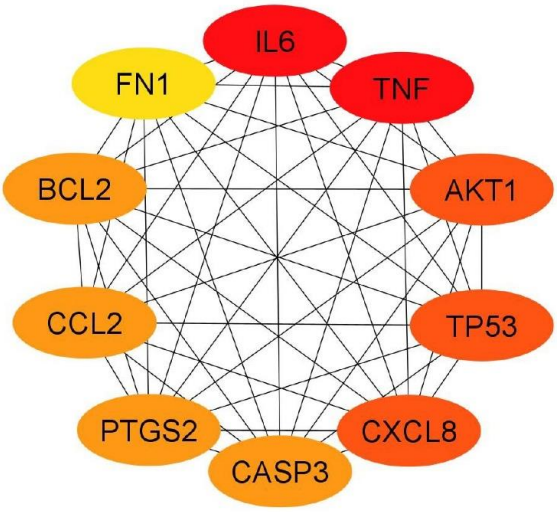

Figure 4. PPI network of 10 core targets of *A. paniculata* against URIs screened by degree. Nodes from light to dark represent the degree value from low to high.

A circular node represents each target, and the nodes are shaded from dark to light. Darker nodes indicate higher degree values, signifying the importance of the corresponding targets. Among them, TNF, IL6 exhibited the highest degree value (degree = 17), followed by AKT1, TP53, CXCL8 (degree = 16), CASP3, PTGS2, CCL2, BCL2 (degree = 15), and FN1 (degree = 14).

The GO enrichment was conducted on 18 overlapping targets, resulting in 187 significant GO terms ($p<0.05$). These terms encompassed 157 entries related to biological processes, 11 entries related to cellular components, and 19 entries related to molecular functions. Among the top 7 biological process terms, the following processes were highly enriched: inflammatory response (GO:0006954), cellular response to lipo-

polysaccharide (GO:0071222), response to xenobiotic stimulus (GO:0009410), positive regulation of gene expression (GO:0010628), response to glucocorticoid (GO:0051384), positive regulation of peptidyl-serine phosphorylation (GO:0033138), and angiogenesis (GO:0001525). These biological processes were closely associated with specific molecular functions, including protease binding (GO:0002020), enzyme binding (GO:0019899), identical protein binding (GO:0042802), protein kinase activity (GO:0004672), protein homodimerization activity (GO:0042803), protein kinase binding (GO:0019901), and protein binding (GO:0005515). Furthermore, these processes primarily occurred in specific cellular locations, such as macromolecular complex (GO:0032991), extracellular region (GO:0005576), endoplasmic reticulum lumen (GO:0005788), cytoplasm (GO:0005737), nucleoplasm (GO:0005654), membrane raft (GO:0045121), and extracellular space (GO:0005615). The top 10 GO terms were visualized and are presented in Fig. 5.

The KEGG pathway enrichment analysis revealed that the 18 overlapping targets were significantly enriched in 89 signaling pathways ($p < 0.01$). To visualize the results, a bubble diagram was created, selecting the top 15 pathways (Fig. 6). The main KEGG pathways included the TNF signaling pathway (hsa04668), IL-17 signaling pathway (hsa04657), and human cytomegalovirus infection (hsa05163). The size of the bubble represents the number of genes enriched in the pathway, while the color intensity indicates the significance of the enrichment (with greener colors indicating smaller FDR and more significant results).

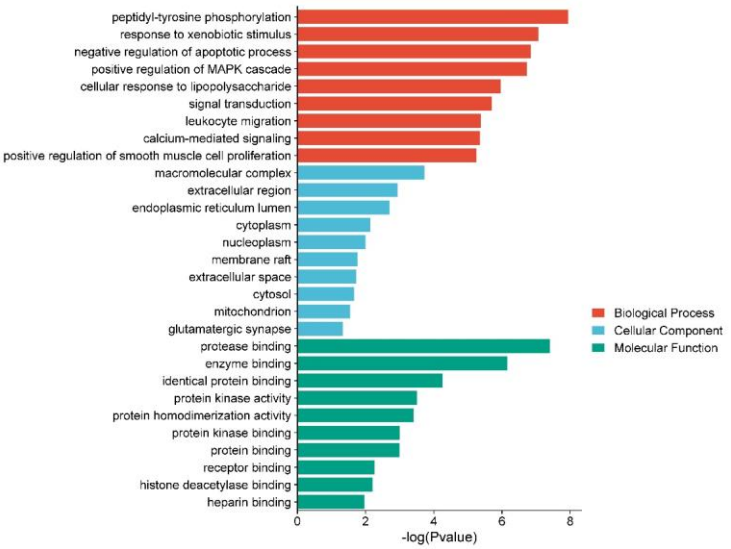

Figure 5. The top 10 results of GO enrichment analyses for 18 overlapping targets.

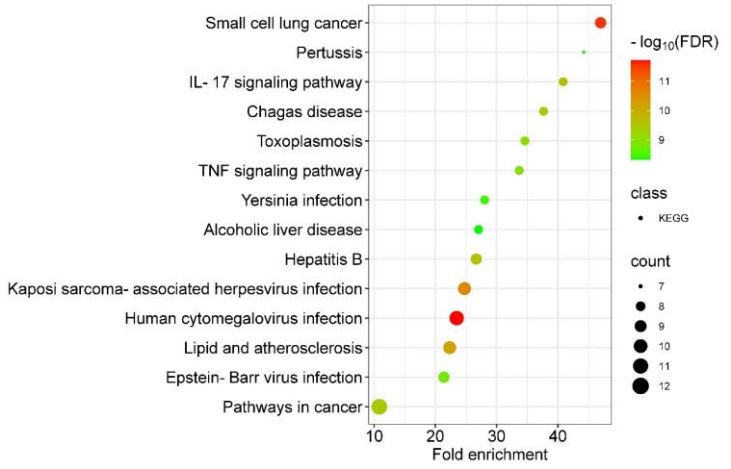

Figure 6. The top 15 results of KEGG pathway enrichment analyses for 18 overlapping targets. The color represents the different $-\log_{10}$ (FDR), the size of the circle represents the gene counts.

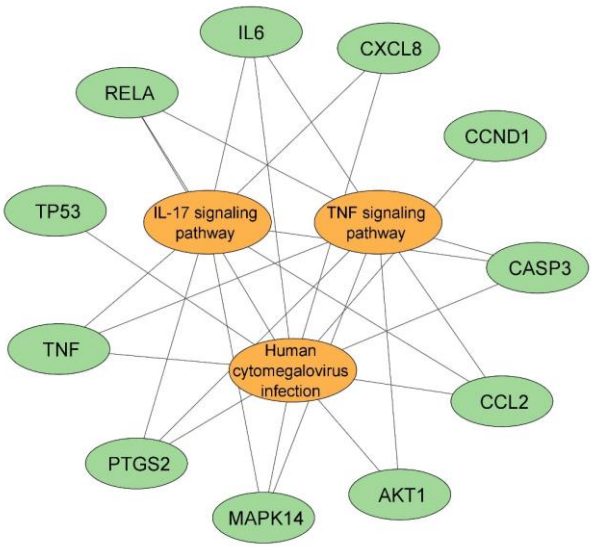

Figure 7. Three main pathways and hub genes.

Table 2. Docking results of the key compounds with hub target proteins.

Key compounds	Docking affinity with hub target proteins (kcal/mol)						
	TNFR1	**IL6**	**AKT1**	**TP53**	**CXCL8**	**CASP3**	**PTGS2**
Wogonin	-9.2	-7.2	-9.5	-8.2	-6.6	-7.5	-8.9
Oroxylin A	-7.1	-7.2	-9.4	-7.6	-6.7	-7.6	-9.1
Quercetin tetramethyl(3',4',5,7) ether	-7.0	-6.6	-8.8	-7.1	-6.4	-7.8	-8.1
Andrographin	-6.9	-6.9	-9.5	-8.0	-6.5	-7.4	-8.3
Moslosooflavone	-7.1	-7.2	-9.2	-8.1	-6.5	-7.3	-8.6
Reference drugs							
Naproxen	-7.4	-7.2	-9.5	-7.1	-6.5	-7.1	-8.3
Oseltamivir	-6.2	-5.8	-7.6	-6.7	-5.3	-7.0	-7.0
Amoxicillin	-6.7	-6.5	-8.5	-7.9	-5.4	-7.6	-8.3

To illustrate the association of the regulatory targets of *A. paniculata* with the main pathways (TNF signaling pathway, IL-17 signaling pathway, and human cytomegalovirus infection), the diagram was constructed, illustrating the correlation between the targets and primary pathways (Fig. 7).

Following a network analysis of the interactions between herbs, compounds, and hub target genes, it was found that the major hub target genes include TNF, IL6, AKT1, TP53, CXCL8, CASP3, and PTGS2 (**Fig. 4**). These hub target genes were identified as significant in the network. Additionally, five key compounds from *A. paniculata* were identified as wogonin, oroxylin A, quercetin tetramethyl(3',4',5,7) ether, andrographin, and moslosooflavone (Table 1 and Fig. 2).

Docking modeling analysis

The docking affinities (kcal/mol) of the key compounds and reference drugs, like naproxen (Bassetti et al., 2024), oseltamivir (Peele et al., 2020), amoxicillin (Khan et al., 2020) with hub target proteins (TNFR1, IL6, AKT1, TP53, CXCL8, CASP3, and PTGS2) are presented in Table 2. The compounds wogonin, oroxylin A, quercetin tetramethyl (3',4',5,7) ether, andrographin, and moslosooflavone demonstrated high degrees of binding affinities, with wogonin and andrographin consistently showing high affinities for multiple targets. For comparison, reference drugs (naproxen/anti-inflammation, oseltamivir/antiviral, and amoxicillin/antibacterial) were also assessed.

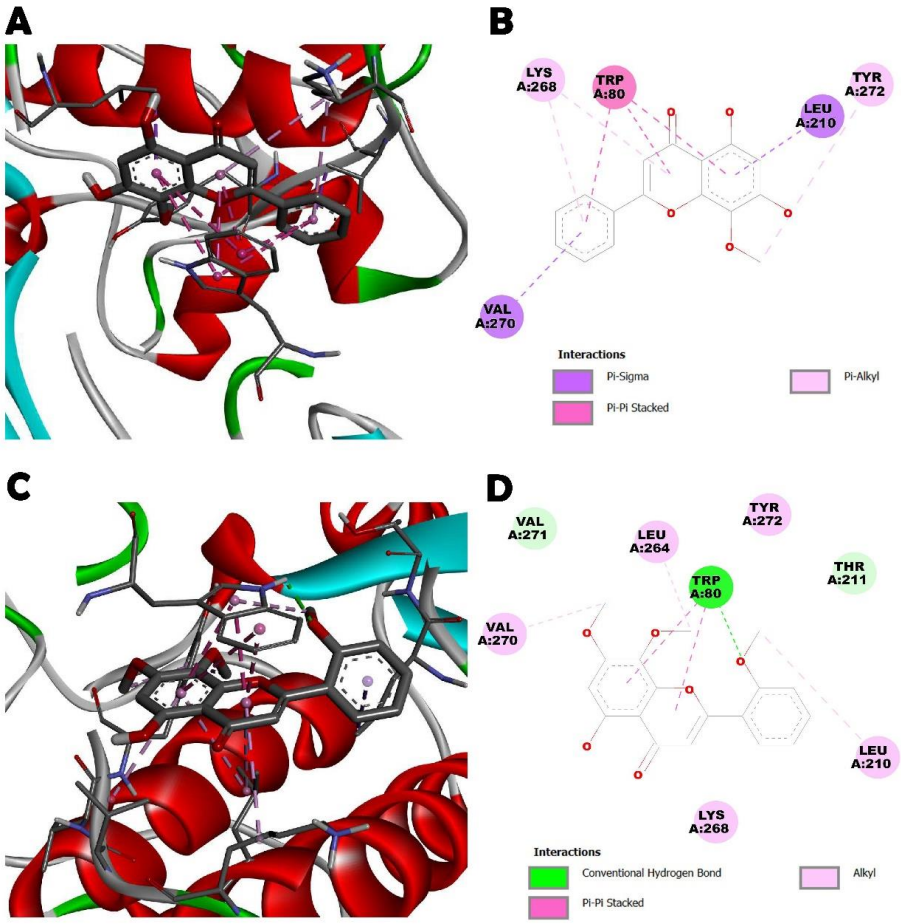

Figure 8. The interaction mechanism of the protein of AKT1 (6HHF) with wogonin was visualized by (A) a 3D diagram and (B) a 2D diagram. The protein of AKT1 (6HHF) with andrographin was visualized by (C) 3D diagram and (D) 2D diagram.

The mean docking scores for TNF, IL6, AKT1, TP53, CXCL8, CASP3, and PTGS2, as well as the key compounds, were -7.46, -7.02, -9.28, -7.8, -6.54, -7.52, and -8.6 kcal/mol, respectively, suggesting robust binding interactions between the compounds and hub target genes. Reference drugs, like naproxen, oseltamivir, and amoxicillin have the mean docking score with hub target genes were -7.59, -6.51, and -7.27 kcal/mol, respectively. TP53 exhibited the strongest binding affinity with wogonin (-8.2 kcal/mol), higher than reference drugs (amoxicillin, -7.9 kcal/mol, and naproxen, -7.1 kcal/mol). AKT1 demonstrated significant affinity with wogonin, andrographin (-9.5 kcal/mol), oroxylin A (-9.4 kcal/mol), and moslosooflavone (-9.2 kcal/mol). Notably, AKT1 showed the highest binding affinity with wogonin, andrographin (affinity = -9.5 kcal/mol), similar results to naproxen, with the docking conformation illustrated in **Fig. 8.** PTGS2 displayed the highest binding affinity with oroxylin A (affinity = -9.1 kcal/mol), wogonin (affinity = -8.9 kcal/mol), and moslosooflavone (affinity = -8.6 kcal/mol), higher than reference drugs (naproxen, amoxicillin, -8.3 kcal/mol and oseltamivir, -7.0 kcal/mol). Naproxen displayed strong binding affinities across multiple targets, rivaling the test compounds. Oseltamivir and amoxicillin were less effective, especially against IL6 and CXCL8, with lower binding affinities (-5.8 to -6.5 kcal/mol).

According to the results of molecular docking, wogonin interacts with the protein AKT1 (6HHF) through pi-sigma interactions with the amino acids Val270 and Leu210, forming 3 pi-pi stacked interactions with Trp80, and forming 3 pi-alkyl interactions with Lys268 and Tyr272. These interactions contribute to stabilizing the protein-wogonin complex with low affinity. The modeling also shows that andrographin interacts with the protein (6HHF) by forming 1 hydro bond with the amino acid Trp80, stabilizing the complex between the ligands and targets. Additionally, andrographin also forms 2 pi-pi stacked interactions with Trp80 and 3 alkyl interactions with Val210, Leu264, and Val270 (Fig. 8).

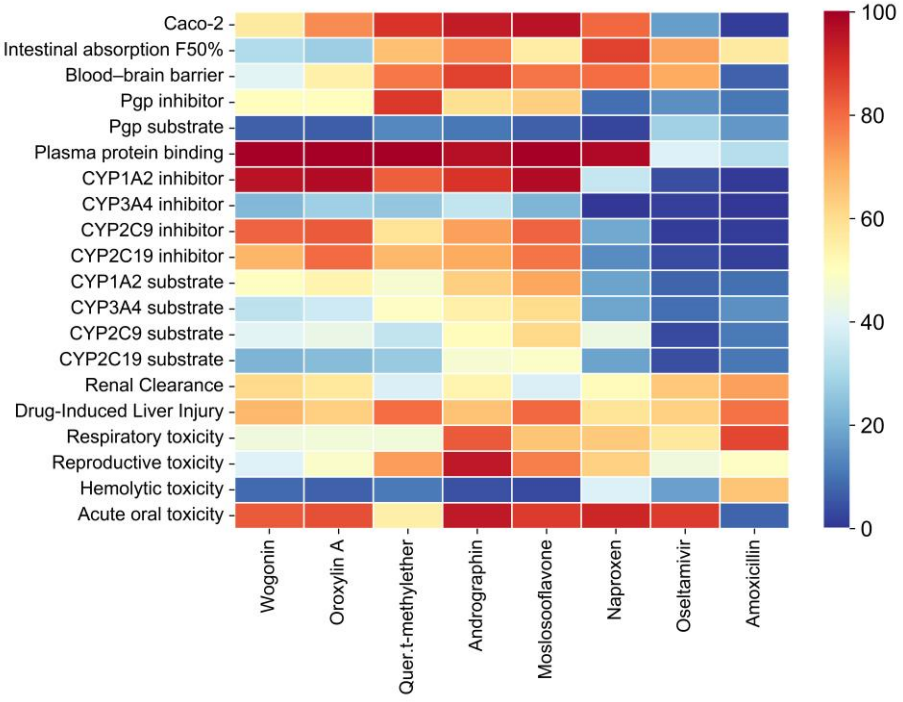

Figure 9. ADMET profiles of key constituents (wogonin, oroxylin A, quer.t-methylether = quercetin tetramethyl(3',4',5,7) ether, andrographin, and moslosooflavone) and reference drugs (naproxen, oseltamivir, and amoxicillin) via heatmap.

ADMET profile of the key constituents

The ADMET characteristics of five key constituents (wogonin, oroxylin A, quercetin tetramethyl(3',4',5,7) ether, andrographin, and moslosooflavone) and reference drugs (naproxen, oseltamivir, and amoxicillin) were predicted using the admetSAR 3.0 web server, with outcomes presented in a heatmap (**Fig. 9**). Quercetin tetramethyl(3',4',5,7) ether, andrographin, and moslosooflavone are expected to show superior caco-2 cell membrane permeability at 89.3%, 94.1%, and 95.9% respectively, equaling or exceeding the reference drug naproxen (probability, 80.5%). Andrographin is particularly projected to display high F50% bioavailability in human intestines (probability, 76.6%), nearing that of naproxen (86.9%). The strongest P-glycoprotein inhibition is anticipated for quercetin tetramethyl(3',4',5,7) ether (88.6%), while other components and reference drugs exhibit minimal inhibitory potential. Furthermore, none of the compounds are predicted to act as P-glycoprotein substrates. In terms of distribution, all active substances are expected to bind to plasma proteins (probability, 96.8-100%), similar to naproxen (97.9%). Regarding metabolism, all active substances are forecasted to inhibit CYP1A2 (82.4-97.5%) and CYP2C19 (67.7-80.4%), in contrast to the reference drugs. Liver injury is anticipated for quercetin tetramethyl(3',4',5,7) ether and moslosooflavone, while andrographin may induce respiratory and reproductive toxicity. Acute oral toxicity is predicted for all active substances and the reference drugs naproxen and oseltamivir, excluding quercetin tetramethyl(3',4',5,7) ether and amoxicillin.

DISCUSSION

Network pharmacology has emerged as a valuable approach for unraveling the biological mechanisms underlying the effects of traditional Chinese medicine formulations. This method constructs complex interaction networks involving bioactive compounds, targets, and biological functions (Luo et al., 2020). This study focused on *A. paniculata*, a plant known for its antimicrobial and anti-inflammatory properties, yet its exact mechanisms still need to be fully understood. Therefore, network pharmacology was employed to analyze the pharmacological mechanisms of *A. paniculata*. Twenty-eight compounds were identified from *A. paniculata* with well-defined chemical structures sourced from common TCM. Through network pharmacological analysis, five key compounds were pinpointed, seven key target genes, and three main pathways responsible for the URIs-therapeutic effect of *A. paniculata*. In the compounds-hub target genes network, five constituents with high degree values stood out: wogonin, oroxylin A, quercetin tetramethyl(3',4',5,7) ether, andrographin, and moslosooflavone. Notably, all these constituents belong to flavonoids, known for their anti-inflammatory, antiviral, and antimicrobial properties.

Wogonin, for instance, has been found to inhibit the replication of various viruses, including influenza viruses and varicella-zoster. It not only suppresses the replication of influenza A virus strains but also reduces the plaque formation of influenza B strains, indicating its broad-spectrum antiviral effects. Moreover, wogonin exhibits inhibition of shingles virus replication by modulating interferon signaling and adenosine monophosphate-activated protein kinase activity. Additionally, wogonin has been confirmed to reduce the activity of enzymes associated with inflammation, such as lipoxygenases and cyclooxygenases (COX) (Chi et al., 2003; Choi et al., 2015; Seong et al., 2018). Previously, studies have demonstrated that pretreatment with oroxylin A inhibits lipopolysaccharide (LPS)-induced mRNA and protein expression of COX-2 and iNOS. Additionally, oroxylin A suppresses NO production. This compound also exhibits potent activity against the influenza A virus both in vitro and in vivo by inhibiting virus protein replication during the biosynthesis stage of the virus life cycle and displaying neuraminidase (NA) inhibition activity. Moreover, oroxylin A promotes interferon production inhibits viral replication, and regulates the host's immune response (Jin et al., 2018; Shimizu et al., 2018; Ye et al., 2014). Pharmacologically, quercetin tetramethyl(3',4',5,7) ether is recognized as a potent anti-inflammatory agent (Horigome et al., 2014). Andrographin can inhibit bacterial activity against sensitive and multidrug-resistant strains of *Mycobacterium tuberculosis* (Boniface and Ferreira, 2020). Moslosooflavone is known to inhibit the activity of adenosine 3,5-cyclic monophosphate phosphodiesterase and significantly suppress the release of PGE2 and NO in LPS-stimulated J774A.1 macrophages. It reduces levels of macrophage inflammatory protein-2, NO, and TNF-α in LPS/IFN-γ-stimulated RAW 264.7 (Chandrasekaran et al., 2011; Chao et al., 2010; Nikaido et al., 1981).

Previous research has demonstrated that certain key compounds found in *A. paniculata* exhibit effectiveness against viruses, bacteria, and inflammation. These findings suggest that these compounds contribute to *A. paniculata*'s therapeutic effects in combating viral, and bacterial infections and reducing inflammation. In a PPI network analysis, seven hub genes, including TNF, IL6, AKT1, TP53, CXCL8, CASP3, and PTGS2, were identified as major targets through which *A. paniculata* exerts its therapeutic effects. Notably, TNF, a proinflammatory cytokine, emerged as a significant hub gene with the highest degree of connectivity (Garrido-Suárez et al., 2023). Recent studies have highlighted TNF's beneficial role in acquired host immunity, particularly in bacterial defense against *Klebsiella pneumonia* and *Brucella abortus* infections (Hop et al., 2017; Laichalk et al., 1996). Additionally, TNF is crucial in the host's antiviral response, mediated through its receptors. These insights underscore the importance of TNF as a key mediator of *A. paniculata*'s therapeutic effects against infections (Ruby et al., 1997).

Gene Ontology (GO) analysis revealed that the hub target genes primarily participate in biological processes such as inflammatory response, cellular response to lipopolysaccharide, and glucocorticoid response. This suggests that *A. paniculata*'s therapeutic effects may involve modulating these processes. Furthermore, the KEGG pathway enrichment analysis indicated that *A. paniculata* likely exerts its therapeutic effects by regulating the IL-17 signaling pathway, TNF signaling pathway, and human cytomegalovirus infection. These findings suggest specific molecular mechanisms through which *A. paniculata* may exert its anti-inflammatory and antiviral effects.

The TNF signaling pathway initiates an inflammatory response primarily by stimulating the activation of inflammatory genes through the MAPK and NF-κB signaling pathways. TNF-α signaling occurs through two cellular receptors, TNF receptor (TNFR)-1 and TNFR-2. Various intracellular antiviral pathways are activated upon interaction with these receptors in response to invading infectious agents. The TNF and TNFR signaling pathway plays a crucial role in the differentiation of T cells, induction of cytokines and chemokines, recruitment of leukocytes, and formation of granulomas, which are essential for controlling virulent bacterial infections (Rahman and McFadden, 2006; Wajant and Siegmund, 2019).

The IL-17 pathway is believed to regulate inflammatory responses that connect systemic diseases with psoriasis. This pathway and its products play a significant role in the inflammation associated with psoriasis. Recognizing its role in disease pathology, the IL-17 pathway has become a target for therapeutic interventions in psoriasis. Currently, three biologic therapies—ixekizumab, secukinumab, and brodalumab—targeting the IL-17 pathway have received FDA approval for treating moderate to severe plaque psoriasis. Activation of the IL-17 signaling pathway has been linked to promoting pyroptosis in pneumonia-induced sepsis, as NK-κB activation can facilitate caspase-1-dependent pyroptosis. These findings suggest a potential role of the IL-17 pathway in promoting inflammatory responses associated with certain diseases, including sepsis (Li et al., 2020; Mosca et al., 2021).

The human cytomegalovirus (HCMV) infection pathway may provide insights into how *A. paniculata* treats diseases associated with viral infections. HCMV, a common herpes virus, triggers an immune

response to combat the virus. However, HCMV has developed mechanisms to infect various hematopoietic cells, evade immune detection, and particularly monocytes. Additionally, HCMV can produce proteins similar to receptors coupled with host proteins, facilitating viral replication and persistence. Initially, targeting viral proteins during infection may not effectively control HCMV and could potentially worsen the infection. Following HCMV infection, there is an overexpression of monocyte chemoattractant protein (MCP), resulting in tissue harm and heightened inflammation, particularly in vascular tissues. These insights suggest potential mechanisms through which *A. paniculata* may counteract viral infections and mitigate associated inflammatory responses (Boomker et al., 2006; Froberg et al., 2001; Simpson et al., 2016).

As a result, *A. paniculata* may influence these pathways to alleviate inflammatory responses and enhance immune function, potentially explaining its observed effects. These KEGG pathways, associated constituents, and hub genes likely interact to produce a combined effect. The results have been validated using docking modeling between the main components (wogonin, oroxylin A, quercetin tetramethyl(3',4',5,7) ether, andrographin, and moslosooflavone) and hub genes (TNF, IL6, AKT1, TP53, CXCL8, CASP3, and PTGS2). The docking affinities of the ligand-protein complexes with values less than -6.0 kcal/mol indicate good binding interactions between the compounds and their target genes (Jegal et al., 2019). Among the compounds studied, wogonin emerges as the most promising due to its consistently high affinity for multiple targets, indicating potential therapeutic uses, particularly in pathways involving AKT1 and TNFR1. The strong interaction of oroxylin A and wogonin with PTGS2 suggests they may possess anti-inflammatory properties, which aligns with their known pharmacological effects. For the reference drugs, naproxen proved to be a robust comparator, especially against inflammatory targets such as TNFR1 and PTGS2. In contrast, oseltamivir and amoxicillin showed limited efficacy, confirming their specificity for viral and bacterial targets, respectively. The ADMET analysis reveals that most key constituents exhibit good permeability through the gastrointestinal mucosa, ensuring effective absorption and distribution of active ingredients to their sites of action. This suggests that *A. paniculata* has the potential to be developed into convenient oral medications for treating URIs. Quercetin tetramethyl(3',4',7) ether demonstrates the ability to inhibit P-glycoprotein and substances that are not P-glycoprotein substrates, leading to increased concentrations of compounds in target cells and tissues, thereby enhancing the bioavailability or potency of medicinal herbs (Nguyen et al., 2021).

Overall, the findings comprehensively understand the potential pharmacological mechanisms underlying *A. paniculata*'s actions and guide additional research and clinical uses. Nevertheless, it's essential to acknowledge limitations. Firstly, the evidence backing the antiviral and anti-inflammatory properties of key compounds and major hub target genes primarily stems from recent cellular or animal studies. Secondly, while the key target proteins expressed by the hub target genes show affinity with the key constituents of *A. paniculata*, their interaction requires experimental validation. In conclusion, while this study presents new insights into the pharmacological mechanisms of *A. paniculata*, further experimental or clinical validation is necessary to confirm the results.

CONCLUSION

This research reveals the potential therapeutic benefits of *A. paniculata* in addressing upper respiratory infections (URIs). The study identified five crucial flavonoid compounds: wogonin, oroxylin A, quercetin tetramethyl ether, andrographin, and moslosooflavone. These constituents showed robust binding affinities with essential target proteins, indicating substantial anti-inflammatory, antiviral, and antimicrobial capabilities. Analysis of pathways connected *A. paniculata*'s effects to the IL-17 and TNF signaling pathways, as well as human cytomegalovirus infection. The compounds' favorable absorption and bioavailability characteristics support their development into oral URI treatments. This investigation underscores the molecular foundation of *A. paniculata*'s effectiveness and endorses its application as a natural remedy for managing URIs, with possibilities for future clinical use.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Thi Duong TL	Thi Phan TT	Nguyen VH	Nguyen ML	Nguyen DK
Concepts or ideas					x
Design	x			x	x
Definition of intellectual content					x
Literature search	x	x			
Experimental studies					
Data acquisition		x		x	x
Data analysis	x		x		x
Statistical analysis			x		
Manuscript preparation	x		x		
Manuscript editing		x			x
Manuscript review	x	x	x	x	x

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