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Molecular Docking and Network Pharmacology Based Approach to Explore Potential Targets for Chikungunya Virus

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I. INTRODUCTION

Chikungunya virus (CHIKV), an arthropod-borne alphavirus, has emerged as a significant public health concern due to its rapid global spread and the debilitating nature of its associated disease. Transmitted primarily by Aedes mosquitoes, CHIKV infection leads to chikungunya fever, characterized by acute febrile illness, rash, and severe polyarthralgia. While the acute phase is often self-limiting, a substantial proportion of patients experience persistent joint pain and arthritis, leading to chronic morbidity.

The CHIKV genome is a single-stranded, positive-sense RNA approximately 11.8 kb in length, encoding four non-structural proteins (nsP1–nsP4) involved in viral replication and five structural proteins (C, E3, E2, 6K, and E1) responsible for virion assembly and host cell entry. Among these, nsP2 functions as a protease critical for processing the viral polyprotein and modulating host antiviral responses, making it a promising target for antiviral drug development. Similarly, the envelope glycoproteins E1 and E2 play crucial roles in viral attachment, fusion, and entry into host cells.

Recent advances in computational biology have facilitated the identification of potential antiviral compounds through molecular docking studies. Virtual screening and docking analyses have identified small molecules with high binding affinity to the active sites of CHIKV proteins, suggesting their potential as inhibitors. For instance, natural compounds such as curcumin, quercetin, and EGCG have demonstrated promising antiviral activities in docking studies. Moreover, FDA-approved drugs like ribavirin and sofosbuvir have been repurposed for potential use against CHIKV.

Beyond targeting viral proteins directly, network pharmacology offers a systems-level approach to understand virus-host interactions and discover additional therapeutic targets. By constructing protein-protein interaction (PPI) networks and integrating molecular docking results, researchers can identify key hubs and pathways modulated during infection. Network analysis techniques, such as clustering and centrality measurements, help prioritize targets with functional significance.

Given the multifaceted nature of CHIKV pathogenesis and the limitations of single-target therapies, a combined strategy utilizing molecular docking and network pharmacology holds significant promise for discovering effective antivirals. This thesis applies an integrative computational approach to identify and validate novel therapeutic targets and compounds against CHIKV infection.

II. MATERIALS AND METHOD

1. Data Collection: By the below steps:

Screening of Active Antiviral Phyto-constituents, Pharmacokinetic ADME Prediction, Potential Target Screening for Anti-Viral Phyto-constituents and CHIKV, BindingDB Database, KEGG Mapper Database, DisGeNET database, Intersection of phytoconstituent and disease target, String Database, Metascape Database,

2. DATA PREPARATION: By the below steps:

Molecular Docking, The preparation of small molecule ligand files, The preparation of macromolecule receptor files, The construction of

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mating pockets, Docking and Visualization, Network Construction, Intersection of Phyto-constituents and Targets, Protein Protein Interaction, Gene Ontology Functional Enrichment.

Bioinformatics Analysis: Molecular Docking & ADME Prediction

Molecular Docking
- Investigates interactions between phytoconstituents (ligands) and target proteins (e.g., spike protein).
- Identifies binding affinities and amino acid interactions.

Pharmacokinetic ADME Prediction (SwissADME)
1. Physicochemical Properties
- Includes molecular weight, H-bond donors/acceptors, rotatable bonds, TPSA, and molar refractivity.

2. Lipophilicity
- Measured via log P (partition coefficient) using models (XLOGP3, WLOGP, MLOGP, SILICOS-IT, iLOGP).
- Higher log P = greater lipophilicity.

3. Solubility
- Predicted using ESOL, SILICOS-IT models (log S scale: insoluble < -10, highly soluble > 0).

4. Pharmacokinetics (BOILED-Egg Model)
- White region (Egg): High GI absorption.
- Yellow region (Yolk): Likely brain permeability.

5. Lipinski's Rule of Five (Ro5)
Oral bioavailability is likely compromised if:
- Log P > 5
- H-bond donors > 5
- H-bond acceptors > 10
- Molecular weight > 500

This analysis helps evaluate drug-likeness and optimize lead compounds in drug discovery.

Table 1. General Characteristics of Phytoconstituents

Sr. No	Compound	Pubchem ID	Molecular Weight (g/mol)	Molecular Formula	Cannocial smiles
1	Amentoflavone	5281600	538.5	$C_{30}H_{18}O_{10}$	C1=CC(=CC=C1C2=CC(=O)C3=C(O2)C(=C(C=C3O)O)C4=C(C=CC(=C4)C5=CC(=O)C6=C(C=C(C=C6O5)O)O)O)O
2	Baicalein	5281605	270.24	$C_{15}H_{10}O_5$	C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O
3	Fisetin	5281614	286.24	$C_{15}H_{10}O_6$	C1=CC(=C(C=C1C2=C(C(=O)C3=C(O2)C=C(C=C3)O)O)O)O

NETWORK PHARMACOLOGY

Network pharmacology is simply the network of molecular interactions. The network was constructed by the information gathered from various databases. Network analysis focuses on the established network using related technology and extracts useful information which is convenient for further studies.

Cytoscape is a free software for visualization and merge of the complicated networks The network nodes symbolize the Phyto-constituents, targets, genes, pathways and or diseases, while edges show their interactions. The network analyzer used for the evaluation of essential properties of the network. At present, most visualizations of NP are through professional tools such as Cytoscape .

By this steps : Pathway Oriented Network Construction, Disease oriented network construction, Intersection of Phyto-constituents and CHIKV targets, Analysis of Protein-protein Interaction, PPI network analysis and hub gene verification, Module Analysis of Protein-Protein Interaction Network, Gene Ontology Functional Enrichment Analysis.

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III. RESULT

3.1 Molecular Docking

The use of Phyto-constituents has long history but their mechanism and targets are yet unclear. Molecular docking (MD) will give interaction between Phyto-constituents and targets, and it can improve the efficiency of bio-active's research. MD was performed between the Phyto-constituents (ligands) and proteins (receptor) using AutoDock Vina. Results of MD was visualized by using Chimera software. By measuring the affinity score between Phyto- constituents and proteins, binding affinity was measured. Results of the MD was obtained in the form of affinity score. Affinity score has inverse relation with the binding effect.

Table 2. Result of Molecular Docking

Phytoconstituents	3TRK	3GPO
Amentoflavone	-9.5	-9.4
Baicalein	-8.5	-9.6
Fisetin	-9.3	-9.7

The study's findings are presented in terms of binding affinity measured in kcal/mol units. The analysis of phytoconstituent docking with the_3TRK protein indicates that Amentoflavone exhibits the highest binding affinity at -9.8 kcal/mol, and closely followed by Fisetin at -9.7 kcal/mol.

The selection of phytoconstituents was based on a comparative assessment of their affinities with both proteins. Notably, Punicalagin and Chebulagic acid, despite displaying the highest binding affinity with both proteins, were not included in subsequent analyses. This decision stems from the fact that Punicalagin and Chebulagic acid lack certain target components relevant to viral infection when compared to other phytoconstituents.

3.2 Results for pharmacokinetic properties

Pharmaco-kinetic study (absorption, distribution, metabolism, excretion, and toxicity) of the phytoconstituents was studied by using the ADME calculator and AdmetSAR databases Their results were obtained for only those Phyto-constituents that show the highest binding affinity from molecular docking results.

Table 3. ADME prediction for phytoconstituents with the highest binding affinity score

Phytoconstituents	**Molecular Wt. (gm/mol)**	**MLOGP**	**H-bond acceptors**	**H-bond Donors**
Amentoflavone	538.46	0.25	10	6
Baicalein	270.24	0.52	5	3
Fisetin	286.24	-0.03	6	4

According to the Lipinski Rule of Five, baicalein, fisetin, follow the rule, whereas amentoflavone violate three parameters: molecular weight, H-bond acceptors, and H- bond donors

3.3 Results for Network Pharmacology

These networks give insight into new drug-diseas associations and their molecular connections through the pathway as well as disease-oriented networks. There are various network measures that gives brief insight about role of individual nodes in the network or about the whole network. Cytoscape software has very easy in-built function that calculates all the most popular measures in one.

Table 4. Network construction result of Amentoflavone

Average Shortest Path Length	**Betweenness Centrality**	**Closeness Centrality**	**Neighborhood Connectivity**
5.094506324	0.00248388	0.196328404	6.666666667
6.080517371	1.37E-05	0.164459633	3
4.3453234545	0.104465959	0.230 125523	6
4.92245622	0.006744759	0.203 166227	4.75
5.045694	0.00248388	0.196328404	6.666666667
4.903245701	0.005 194805	0.204027557	2
3.9045679	0.024065498	0.255813953	19.66666667

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5.82456299	0	0. 16434562	2
4.623456052	0.02529653	0.2146785707	2.142857143
4.06234565	0.011238752	0.24600639	27.5
5.64123449	0	0.173451494	7
5.42345616	0.001741734	0.13456278	5
4.064935065	0.011238752	0.1234559	27.5
5.1123456	0.004757333	0.19323419	11.66666667
5.649350649	0	0.17323494	7
4.698701299	0.017082653	0.21232345	9,5
5.14025974	0.006609	0.19432345	1.666666667
6. 137662338	0	0.1643451	3
4.251948052	0.010102656	0.235178316	23
4.922077922	0.005171324	0.203 166227	6
6.314285714	0	0.158371041	6
6.314285714	0	0.158371041	6
4.542857143	0.013268339	0.220125786	5.333333333
4.454545455	0.01 1436974	0.224489796	5.4
3.914285714	0.029745794	0.255474453	12.14285714
4.574025974	0.030352926	0.21 8625781	3.285714286
5.566233766	9.66E-07	0.17965469	14
5.566233766	9.66E-07	0.17965469	14
5.566233766	9.66E-07	0.17965469	14
5.015584416	0.011024223	0.19937856	9.25
5.566233766	9.66E-07	0.17965469	14
5.566233766	9.66E-07	0.17965469	14
5.566233766	9.66E-07	0.17965469	14
4.87012987	0.007156786	0.20456733	0.204567333
5.566233766	9.78E-07	0.17965469	14
5.566233766	9.65E-07	0.132165469	14
4.4567481	0.01378935	0.22345606	12

Above table represents the results for network pharmacology In the above table, average shortest path length is the average number of steps along the shortest paths for all the possible pairs of network nodes. It is the efficiency of information.

All this information is necessary to read the network construction with the easiest way. The network consists of 488 nodes and 901 edges, where each node represents an effective compound or target name, and each line represents a connection between the two. After further analysis of the topology of the network, it is found that the network has the following characteristics density = 0.008, network centralization = 0.178, network heterogeneity = 1.723. In addition, in the topology analysis of the network, the degree of the node is determined by its connection. Through the analysis, the degree of phytoconstituent was found to be 49. At the same time, we also analyzed the degree of the target and found that the top five degrees of the target were PTGS2 (degree = 11), ABCB1 (degree= 8), MMP9 (degree = 8),' CDK6 (degree = 7), and MET (degree = 6).

Table 5. Network construction result of Baicalein

Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Neighborhood Connectivity
3.338947	0.0091 61	0.299496	53.5
3.322105	0.004934	0.301014	55.5
3.263158	0.008644	0.306452	62.5
3.347368	0.002519	0.298742	52.5
3.94567	0.001453	0.297619	51

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3.3679	0.002145	0.256719	51
3.322105	0.01052	0.301014	55.5
3.351579	3.3534329	0.298367	52
3.3856	0.003423	0.345619	51
3.347368	0.003213	0.298742	52.5
3.343158	0.003251	0.299118	53
3.347368	0.009465	0.297992	52.5
3.355789	0.003987	0.297992	51.5
3.355789	0.002454	0.297992	51.5
3.355789	0.004002	0.297992	51.5
3.343158	0.003109	0.299118	53
3.36	0.008403	0.297619	51
3.330526	0.00351	0.300253	54.5
3.330526	0.007192	0.300253	54.5
3.330526	0.002722	0.300253	54.5
3.330526	0.002532	0.300253	54.5
3.330526	0.002776	0.300253	54.5
3.36	0.003174	0.297619	51
3.330526	0.003062	0.300253	54.5
3.330526	0.002295	0.300253	54.5
3.330526	0.003519	0.300253	54.5
3.330526	0.002476	0.300253	54.5
3.5698	0.003174	0.297619	51
3.235879	0.003174	0.297619	51
3.330526	0.001956	0.300253	54.5
3.330526	0.001956	0.300253	54.5
3.330526	0.001956	0.300253	54.5
3.291317	0.004414	0.30383	43
3.285714	0.003895	0.304348	43.5
3.291317	0.005796	0.30383	43
3.285324	0.002266	0.304348	43.5
0.005796	0.009769	0.308557	47.5
3.313725	0.006133	0.301775	41
3.313725	0.24323	0.301775	41
3.291317	0.003072	0.30383	43
3.229692	0.012345	0.309627	48.5
3.257703	0.004364	0.306965	46
3.302521	0.002334	0.302799	42
3.302521	0.223424	0.302799	42
3.296919	0.03456	0.303314	42.5
3.291317	0.004262	0.30383	43
3.308123	0.00368	0.302286	41.5
3.156863	0.012607	0.31677	55
3.313725	0.011173	0.301775	41
3.190476	0.008343	0.3 13433	52
3.061625	0.023831	0.326624	63.5

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The network consists of 476 nodes and 932 edges, where each node represents an effective compound or target name, and each line represents a connection between the two. After further analysis of the topology of the network, it is found that the network has the following characteristics density = 0.008, network centralization = 0.203, network heterogeneity 1.713. In addition, in the topology analysis of the network, the degree of the node is determined by its connection. Through the analysis, the degree of phytoconstituent was found to be'100. At the same time, we also analyzed the degree of the target and found that the top five degrees of the target were PSMA4 (degree = 11), PSMA3 (degree = 11), ALOX12 (degree= 6), PTGS2 (degree = 6), and MAOB (degree =4).

Table 6. Network construction result of Fisetin

Average Shortest Path Length	**Betweenness Centrality**	**Closeness Centrality**	**Neighborhood Connectivity**
3.285714	0.009779	0.304348	43.5
3.263305	0.003551	0.306438	45.5
3.184874	0.007778	0.3 13984	52.5
3.313725	0.00238	0.301775	41
3.313725	0.002663	0.301775	41
3.263305	0.013459	0.306438	45.5
3.302521	0.002427	0.302799	42
3.3 13725	0.011173	0.301775	41
3.296919	0.007323	0.303314	42.5
3.291317	0.002743	0.30383	43
3.296919	0.005144	0.303314	42.5
3.308123	0.004084	0.302286	41.5
3.291317	0.003376	0.30383	43
3.313725	0.011173	0.301775	41
3.27451	0.003704	0.305389	44.5
3.27451	0.007466	0.305389	44.5
3.196078	0.008688	0.3 12883	51.5
3.302521	0.001954	0.302799	42
3.285714	0.004919	0.304348	43.5
3.291317	0.004414	0.30383	43
3.285714	0.003895	0.304348	43.5
3.291317	0.005796	0.30383	43

The network consists of 358 nodes and 759 edges, where each node represents an effective compound or target name, and each line represents a connection between the two. After further analysis of the topology of the network, it is found that the network has the following characteristics density = 0.012, network centralization = 0213, network heterogeneity = 1.560. In addition, in the topology analysis of the network, the degree of the node is determined by its connection. Through the analysis, the degree of phytoconstituent was found to be 80. At the same time, we also analyzed the degree of the target and found that the top five degrees of the target were PTGS2 (degree= 6), CYP1A1 (degree= 6), ALOX12 (degree =4), VEGFA (degree= 4), and MET (degree = 4).

Upon comparing all the compounds, it is evident that Baicalein, Fiseten, exhibit the greatest degree of freedom. This observation implies that within the group of three phytoconstituents, these particular substances might possess a significant capacity to effectively contribute to the treatment of CHIKV.

3.4 Results for intersection of Phyto-constituents and CHIKV targets

Intersection of predicted targets of the Phyto-constituents and CHIKV disease can provide insightful perspectives of repositioning as wel as repurposing the molecules for new applications The mutual targets for chosen Phyto-constituents and CHIKV disease are as above that may considered as a potential target for further analysis. These obtained mutual predicted " targets were pasted to the tool "Analysis* in Gene Card Analysis database. And, it gives the interactive results with various diseases for various species.

Table 8. Mutual predicted targets of Phyto-constituents and CHIKV disease

Phyto-constituents	Mutual Targets with CHIKV
Amentoflavone	F2
Baicalein	F2;AXL
Fisetin	F2; AXL; GSK3B; HSP90AB1; JAK2; HDAC1; HDAC2; VEFGA

3.5 Results for protein interaction network of targets

For the construction of a protein-protein interaction network, parameters were set to Homo sapiens, and the interactive score was set to the highest credibility. The degree values of nodes and edges in the network were analyzed. Proteins usually regulate their physiological functions through protein interactions and other pathways. To better reveal the mechanism of Phytoconstituents in the treatment of CHIKV, we used STRING V11.0 to construct a protein- protein interacting network. After topology analysis of the PPI network, it is found that

For Amentoflavone, 90 nodes were involved. Number of edges were 465 and average node degree was 10.3. AIso, average local clustering coefficient value was 0.584

For Baicalein, 99 nodes were involved. Number of edges were 521 and average node degree was 10.5. Also, average local clustering coefficient value was 0.587

For Fisetin, 80 nodes were involved. Number of edges were 318 and average node degree was 7.95. Also, average local clustering coefficient value was 0.488.

Upon analysis, Baicalein, exhibited the greatest degree of freedom relative to other phytoconstituents. This observation implies their potential significance in the treatment of the chikungunya virus.

3.6 Results for PPI network analysis and hub gene verification

CytoHubba plug-in in Cytoscape software was used for screening the top 10 hub genes. Hubs are defined as the most connected nodes within the network thus they are responsible to sustain network connectivity.

Table 9. Top ten hub genes of Phyto-constituents

Phytoconstituents	Top ten hub genes
Amentoflavone	ESR1, VEGFA, EGFR, PTGS2, SNCA, CYP3A4, CFTR, AR, MMP9. PSMA4.
Baicalein	ESR1, VEGFA, EGFR, PTGS2, SNCA, AR, MMP9, PSMA4, CFTR. PPARG.
Fisetin	ESRI, VEGFA, EGFR, PTGS2, SNCA, PPARG, AR, MMP9, CFTR,PSMA4.

- ESR1 (Estrogen Receptor Alpha): Mediates the body's response to estrogen, regulating physiological processes.
- VEGF-A (Vascular Endothelial Growth Factor A): Promotes angiogenesis (new blood vessel formation).
- EGFR (Epidermal Growth Factor Receptor): Regulates cell growth, proliferation, survival, and differentiation.
- PTGS2 (COX-2): Produces prostaglandins, involved in inflammation and physiological processes.
- SNCA (Alpha-Synuclein): Regulates synaptic function and neurotransmitter release in the brain.
- CYP3A4: Metabolizes drugs, toxins, and endogenous compounds.
- CFTR (Cystic Fibrosis Transmembrane Conductance Regulator): Controls chloride ion movement across cell membranes.
- AR (Androgen Receptor): Mediates effects of testosterone and DHT.
- MMP-9 (Gelatinase B): Involved in tissue remodeling and wound healing.
- PSMA4 (Proteasome Subunit Alpha-4): Part of the proteasome, degrades damaged proteins.
- PPARG (PPARγ): Regulates fat cell differentiation, glucose, and lipid metabolism.
- PRKCA & PRKCB (PKCα & PKCβ): Serine/threonine kinases involved in cell signaling and growth.
- AKR1B1 (Aldose Reductase): Metabolizes glucose and other sugars.
- TRPC1 & TRPC4: Ion channels regulating calcium and sodium flow in cells.
- HSP90AB1 (Heat Shock Protein 90): Helps in protein folding and stabilization.
- APP (Amyloid Precursor Protein): Involved in neuronal development and maintenance.
- PTPN1 (PTP1B): Negatively regulates tyrosine kinase signaling.
- PSMA3 & PSMB10: Proteasome subunits that degrade ubiquitin-tagged proteins.

3.7 Results for Module Analysis of Protein-Protein Interaction Network

Proteins often work together in functional modules. Using MCODE, we analyzed protein-protein interaction (PPI) networks to identify key functional modules, where nodes represent targets and edges represent interactions.

Key Findings:

Amentoflavone

Module 1 (Score: 15.6): 16 nodes, 117 edges (e.g., PSMB6, SNCA, PSMA1).
Module 2 (Score: 8.0): 8 nodes, 28 edges (e.g., KIT, ESR1, TERT).
Module 3 (Score: 5.0): 5 nodes, 10 edges (e.g., PLA2G10, ALOX12, PLA2G5).

Baicalein

Module 1 (Score: 16.5): 17 nodes, 132 edges (e.g., PSMB8, SNCA, PSMA5).
Module 2 (Score: 6.429): 15 nodes, 45 edges (e.g., APP, PTPN1, KDR).
Module 3 (Score: 4.545): 12 nodes, 25 edges (e.g., ABCB1, AKR1C3, MET).
Module 4 (Score: 3.692): 14 nodes, 24 edges (e.g., TERT, PARP1, CDK6).

Fisetin

Module 1 (Score: 4.00): 4 nodes, 6 edges (e.g., PRKCH, PRKCB, PRKCA).
This analysis helps uncover key protein interactions and potential mechanisms of action.

3.8 Results for Gene Ontology Functional Enrichment Analysis

For Amentoflavone,

Table 10. Biological process analysis of Amentoflavone,

Pathway	Genes
Proteasome	PSMA4 PSMA3 PSMB5 PSMA6 PSMA2 PSMB2 PSMA1 PSMB6 PSMA5 PSMB4 PSMB10
Nitrogen metabolism	CA2 CA4 CA7
Ovarian steroidogenesis	PTGS2 HSDI7B2 HSDI7B1 CYP19A1 CYPIBI IGFIR CYPIA1
Tryptophan metabolism	MAOB CYP1B1 CYPIA1 CYP1A2 MAOA
Phenylalanine metabolism	MAOB MAO

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Table 11. Cellular component analysis of Amentoflavone

Pathway	Genes
Proteasome core complex	PSMA4 PSMA3 PSMB5 PSMA6 PSMA2 PSMB2 PSMA1 PSMB6 PSMA5 PSMB4 PSMB10
Proteasome core complex, beta-subunit complex	PSMB5 PSMB2 PSMB6 PSMB4 PSMB10
Endopeptidase complex	PSMA4 PSMA3 PSMB5 PSMA6 PSMA2 PSMB2 PSMA1 PSMB6 PSMA5 PSMB4 PSMB10
Protein kinase CK2 complex	CSNK2A1 CSNK2A3
Peptidase complex	PSMA4 PSMA3 PSMBS PSMA6 PSMA2 PSMB2 PSMA1 PSMB6

Table 12. Molecular function analysis of Amentoflavone

Pathway	Genes
Carbonate dehydratase activity	CA12 CA2 CA4 CA7
Threonine-type endopeptidase activity	PSMA4 PSMB5 PSMB2 PSMB6 PSMB4 PSMB10
Transcription coactivator binding	ESR1 AHR TERT PPARA
BH domain binding	MCL1 BCL2
Death domain binding	MCL1 BCL2

For Baicalein,

Table 13. Biological process analysis of Baicalein

Pathway	Genes
Proteasomal ubiquitin- independent protein catabolic proc.	PSMA4 PSMA3 PSMB5 PSMA6 PSMA2 PSMB2 PSMA1 PSMB6 PSMA5 PSMB4 PSMB10
Cyclooxygenase pathway	PTGS2 CBR1 AKRIC3
Pos. reg. of membrane depolarization	ALOX12 KDR PARP1
Neurotransmitter catabolic process	MAOB ACHE MAOA

Table 14. Cellular component analysis of Baicalein

Pathway	Genes
Proteasome core complex	PSMA4 PSMA3 PSMB5 PSMA6 PSMA2 PSMB2 PSMAI PSMB6 PSMAS PSMB4 PSMB10
Proteasome core complex, beta-subunit complex	PSMB5 PSMB2 PSMB6 PSMB4 PSMB10
Nuclear cyclin-dependent protein kinase holoenzyme complex	CCNTI CDK9
Endopeptidase complex	PSMA4 PSMA3 PSMB5 PSMA PSMA2 PSMB2 PSMAI PSMB6 PSMAS PSMB4 PSMB10
Protein kinase CK2 complex	CSNK2A1 CSNK2A3

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Table 15. Molecular function analysis of Baicalein

Pathway	Genes
Carbonate dehydratase activity	CA12 CA2 CA4 CA7
RNA polymerase II CTD heptapeptide repeat kinase activity	CDK6 CDK9 CDK1
Testosterone dehydrogenase (NAD+) activity	HSDI7B2 HSDI7B1 AKRIC3
Threonine-type endopeptidase activity	PSMA4 PSMB5 PSMB2 PSMB6 PSMB4 PSMB10
Transcription coactivator binding	ESRI AHR CDK9 TERT

For Fisetin,

Table 16. Biological process analysis of Fisetin

Pathway	Genes
Cyclooxygenase pathway	PTGS2 CBRI AKRIC3
Pos. reg. of membrane depolarization	ALOX12 KDR PARPI
Neurotransmitter catabolic proc.	MAOB ACHE MAOA
Lipoxygenase pathway	PTGS2 ALOX12 ALOX15 ALOX15B
Mast cell chemotaxis	VEGFA PGF KIT

Table 17. Cellular component analysis of Fisetin

Pathway	Genes
Nuclear cyclin-dependent protein kinase holoenzyme complex	CCNT1 CDK9
Protein kinase CK2 complex	CSNK2A1 CSNK2A3
Cyclin-dependent protein kinase holoenzyme complex	CDK6 CDK2 CCNTI CDK9 CDKI
Nuclear outer membrane	PTGS2 SNCA
Carboxy-terminal domain protein kinase complex	CNTI CDK9

Table 18. Molecular function analysis of Fisetin

Pathway	Genes
Carbonate dehydratase activity	CAI2 CA2 CA4 CA7
RNA polymerase I CTD heptapeptide repeat	CDK6 CDK9 CDK1
kinase activity	
Testosterone dehydrogenase (NAD+) activity	HSDI7B2 HSD17B1 AKRIC3
Alditol:NADP+ 1- oxidoreductase activity	AKR1B1 AKRIC3
Hydrolase activity, acting on ether bonds	ALOX12 ALOX15

Through the functional enrichment analysis of GO of GO, the main functions of the targets are enriched to Proteasome core complex, Proteasomal ubiquitin-independent protein catabolic process, Carbonate dehydratase activity, Cyclooxygenase pathway and so on. Among them, the two functions f Proteasomal ubiquitin-independent protein catabolic process, Cyclooxygenase pathway activity are enriched to the most genes with high significance, so they may imply that they are the main functions of the target.

CONCLUSION

In this study, the molecular mechanism of Phytoconstituents in the treatment of chikungunya virus was explored by means of network pharmacology and molccular docking. It was found that the potentially important Phytoconstituents in the treatment of chikungunya virus were Fisetin, and Baicalein. Through the PPI network analysis, it is found that the potential Phytoconstituents in the treatment of chikungunya virus are Baicalein and the network can be divided into three modules. GO functional enrichment analysis showed that the target mainly performed Proteasomal ubiquitin-independent protein catabolic process and other functions. Finally, it is of great significance to test and explore the binding between the active components and the target by means of molecular docking. Further study on the antiviral activity of phytoconstituents and the underlying mechanism are still urgently to be investigated in other methods such as in vitro, in vivo, and clinical study evaluation to verify this in silico study.

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