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Network Pharmacology Analysis of Naringenin Against Psoriasis

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Abstract: *Psoriasis is a chronic inflammatory autoimmune skin disorder characterized by abnormal keratinocyte proliferation, angiogenesis, oxidative stress, and immune dysregulation. Naringenin, a naturally occurring flavanone commonly found in citrus fruits, possesses significant anti-inflammatory, antioxidant, and immunomodulatory properties. The present study aimed to investigate the therapeutic potential and molecular mechanisms of Naringenin against psoriasis using a network pharmacology approach. The chemical and pharmacokinetic properties of Naringenin were collected from public databases, and potential molecular targets were predicted using bioinformatics tools. Psoriasis-associated genes were retrieved from disease databases, and overlapping targets between psoriasis and Naringenin were identified. Protein–protein interaction (PPI) analysis, Gene Ontology (GO) enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed to explore the biological significance of the common targets. A total of several overlapping targets were identified, including VEGFA, PPARG, MMP9, PIK3CA, SRC, PTGS1, MMP2, and NOX4. Network analysis revealed VEGFA, PPARG, MMP9, PIK3CA, and SRC as major hub targets involved in psoriasis progression. GO and KEGG enrichment analyses indicated that the targets were mainly associated with inflammatory response, angiogenesis, apoptosis, oxidative stress, PI3K-Akt signaling pathway, MAPK signaling pathway, VEGF signaling pathway, and cytokine-mediated pathways. The findings suggest that Naringenin may exert anti-psoriatic effects through multi-target and multi-pathway mechanisms involving regulation of inflammation, keratinocyte proliferation, immune response, and angiogenesis. This study provides a scientific basis for the potential application of Naringenin as a promising therapeutic candidate for psoriasis management and highlights the importance of further experimental validation.*

Keywords: Psoriasis; Naringenin; Network Pharmacology; Molecular Targets; VEGFA; PPARG; MMP9; PI3K-Akt Signaling Pathway; Inflammation; Flavanone; GO Enrichment Analysis; KEGG Pathway Analysis; Protein–Protein Interaction Network; Natural Compounds; Bioinformatics

I. INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by abnormal keratinocyte proliferation, erythematous plaques, scaling, and persistent inflammation. It affects nearly 2–3% of the global population and significantly impairs the quality of life of affected individuals. The disease is associated not only with cutaneous manifestations but also with systemic complications such as psoriatic arthritis, cardiovascular disorders, metabolic syndrome, obesity, and depression. The pathogenesis of psoriasis is highly complex and involves genetic susceptibility, environmental triggers, oxidative stress, immune dysregulation, and abnormal activation of inflammatory signaling pathways.[1-3]

The development of psoriasis is strongly associated with the dysregulation of immune cells, particularly T-helper (Th1 and Th17) lymphocytes, dendritic cells, and keratinocytes. These cells produce various pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), interleukin-23 (IL-23), and interleukin-6 (IL-6),

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which collectively contribute to chronic inflammation and excessive epidermal proliferation. Additionally, angiogenesis, oxidative stress, and extracellular matrix remodeling play critical roles in the progression of psoriatic lesions. Despite the availability of conventional therapies such as corticosteroids, immunosuppressants, phototherapy, and biologics, long-term treatment is often associated with adverse effects, high cost, limited efficacy, and disease recurrence. Therefore, the exploration of safer and more effective therapeutic agents remains an important area of research.[4-5]

Natural phytoconstituents have gained considerable attention due to their broad pharmacological activities and relatively lower toxicity. Among them, Naringenin, a flavanone abundantly present in citrus fruits such as oranges, grapefruits, and tomatoes, has emerged as a promising bioactive compound with anti-inflammatory, antioxidant, anti-proliferative, and immunomodulatory properties. Previous studies have demonstrated that Naringenin can regulate inflammatory cytokines, inhibit oxidative stress, suppress angiogenesis, and modulate multiple intracellular signaling pathways including PI3K/Akt, MAPK, NF-κB, and JAK/STAT pathways. These pharmacological activities suggest its potential role in the management of chronic inflammatory diseases, including psoriasis.[6-8]

The therapeutic efficacy of herbal compounds is often mediated through multiple molecular targets and interconnected signaling pathways rather than a single mechanism of action. In this context, network pharmacology has emerged as a powerful systems biology-based approach that integrates pharmacology, bioinformatics, molecular biology, and computational analysis to understand the complex interactions among drugs, targets, pathways, and diseases. Unlike the conventional "one drug–one target" concept, network pharmacology emphasizes the "multi-target–multi-pathway" mode of action, which is particularly relevant for natural compounds and complex diseases such as psoriasis.[9-11]

Therefore, the present study was designed to investigate the molecular mechanisms underlying the anti-psoriatic activity of Naringenin using a network pharmacology approach. The study involved the identification of Naringenin-associated targets, collection of psoriasis-related genes, screening of common targets, construction of protein–protein interaction networks, and enrichment analyses including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses. Furthermore, key hub targets involved in psoriasis progression were identified to better understand the therapeutic potential of Naringenin. The findings of this study may provide a scientific basis for the development of Naringenin as a potential natural therapeutic candidate for psoriasis treatment and support future experimental and clinical investigations.

II. MATERIALS AND METHODS [12-15]

Collection of Naringenin Data

The phytoconstituent Naringenin was selected for the present network pharmacology study based on its reported anti-inflammatory, antioxidant, and immunomodulatory activities. The chemical information of Naringenin, including compound name, molecular formula, molecular weight, canonical SMILES, InChI, and 2D/3D structures, was retrieved from PubChem. The PubChem Compound Identifier (CID) of Naringenin was 439246. Physicochemical, pharmacokinetic, drug-likeness, and medicinal chemistry properties were analyzed using SwissADME.

Prediction of Naringenin-Associated Targets

Potential molecular targets of Naringenin were identified using publicly available target prediction databases including SwissTargetPrediction, PubChem, and ChEMBL. The canonical SMILES structure of Naringenin was used as the input query. Predicted targets with significant probability scores were collected and duplicate entries were removed. The target proteins were standardized using UniProt identifiers obtained from UniProt.

Identification of Psoriasis-Related Targets

Psoriasis-associated genes and therapeutic targets were collected from disease-related databases including GeneCards, DisGeNET, OMIM, and Therapeutic Target Database using the keyword "Psoriasis". All retrieved targets were merged and duplicate genes were removed to obtain a comprehensive psoriasis-associated target dataset.

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Identification of Common Targets

The predicted targets of Naringenin and psoriasis-related genes were compared to identify overlapping targets associated with both the compound and disease. The common targets were identified using Venn diagram analysis. These overlapping targets were considered potential therapeutic targets involved in the anti-psoriatic activity of Naringenin.

Construction of Compound–Target–Disease Network

The interaction network among Naringenin, common targets, and psoriasis was constructed using Cytoscape version 3.10.2. Nodes represented compounds, targets, and disease entities, while edges represented their interactions. Network topology parameters such as degree value, betweenness centrality, and closeness centrality were analyzed to identify major hub targets within the network.

Protein–Protein Interaction (PPI) Network Analysis

The identified common targets were imported into STRING to construct a protein–protein interaction (PPI) network. The species was restricted to *Homo sapiens*, and a confidence score threshold of ≥0.4 was applied. The generated interaction network was exported and further visualized in Cytoscape software. Hub genes were identified based on topological parameters using Cytoscape plug-ins such as CytoHubba.

Gene Ontology (GO) Enrichment Analysis

Functional enrichment analysis of the overlapping targets was performed to determine their biological significance. Gene Ontology (GO) enrichment analysis was carried out under three categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). The enrichment analysis was conducted using DAVID and/or Enrichr. Terms with $p < 0.05$ were considered statistically significant.

KEGG Pathway Enrichment Analysis

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed to identify signaling pathways associated with the common targets. The analysis was conducted using DAVID and Enrichr platforms. Significantly enriched pathways related to inflammation, immune regulation, angiogenesis, oxidative stress, and keratinocyte proliferation were selected for interpretation in psoriasis pathogenesis.

Identification of Key Targets

Based on network topology analysis, PPI interaction scores, and biological relevance in psoriasis, the top hub targets were identified. VEGFA, PPARG, MMP9, PIK3CA, and SRC were selected as the major key targets due to their crucial involvement in angiogenesis, inflammatory signaling, extracellular matrix remodeling, immune activation, and keratinocyte hyperproliferation in psoriasis.

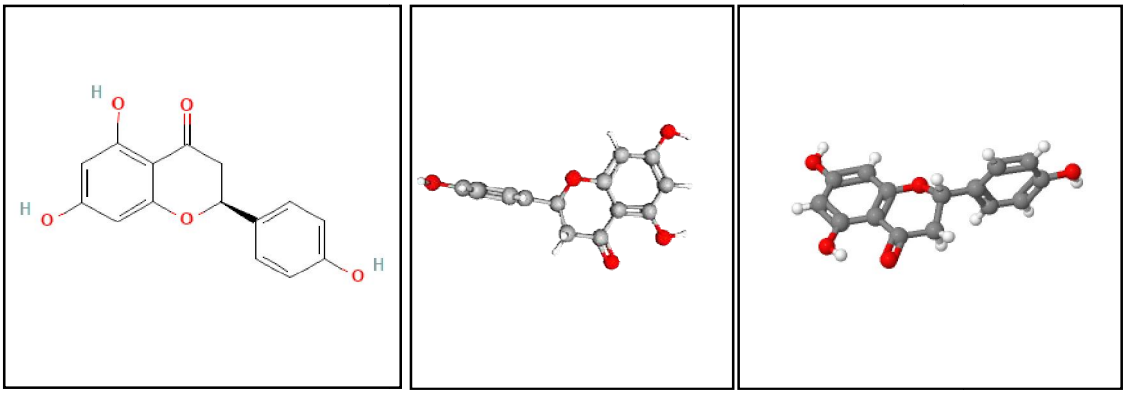

Fig 1: 2D, 3D and Crystal Structures of Naringenin

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Table 1: Property of Naringenin

Property	Description
Compound Name	Naringenin
Compound CID	439246
Molecular Formula (MF)	$C_{15}H_{12}O_5$
Molecular Weight (MW)	272.25 g/mol
IUPAC Name	(2S)-5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one
SMILES	C1[C@H](OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
InChI	InChI=1S/C15H12O5/c16-9-3-1-8(2-4-9)13-7-12(19)15-11(18)5-10(17)6-14(15)20-13/h1-6,13,16-18H,7H2/t13-/m0/s1
InChIKey	FTVWIRXFELQLPI-ZDUSSCGKSA-N
Chemical Class	Flavanone
Source	Commonly found in citrus fruits
PubChem CID	439246

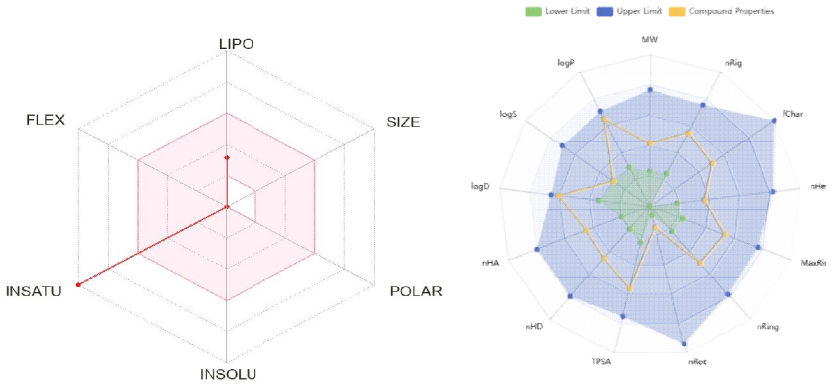

Fig 2: Radar plot of Naringenin Swiss ADME and ADMTE Lab 3.0

Table 2: Physicochemical Properties of Naringenin Swiss ADME

Category	Property	Value
Physicochemical Properties	Num. Heavy Atoms	20
	Num. Aromatic Heavy Atoms	12
	Fraction Csp3	0.07
	Num. Rotatable Bonds	1
	Num. H-bond Acceptors	5
	Num. H-bond Donors	3
	Molar Refractivity	71.57
	TPSA	86.99 Å²
Lipophilicity	Log Po/w (iLOGP)	2.04
	Log Po/w (XLOGP3)	2.50
	Log Po/w (WLOGP)	2.37
	Log Po/w (MLOGP)	-0.03

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	Log Po/w (SILICOS-IT)	2.68
	Consensus Log Po/w	1.91
Water Solubility	Log S (ESOL)	-3.52
	Solubility (ESOL)	8.18e-02 mg/ml ; 3.00e-04 mol/l
	Class (ESOL)	Moderately soluble
	Log S (Ali)	-3.74
	Solubility (Ali)	4.94e-02 mg/ml ; 1.81e-04 mol/l
	Class (Ali)	Soluble
	Log S (SILICOS-IT)	-3.01
	Solubility (SILICOS-IT)	2.66e-01 mg/ml ; 9.77e-04 mol/l
	Class (SILICOS-IT)	Soluble
Pharmacokinetics	GI Absorption	High
	BBB Permeant	No
	P-gp Substrate	No
	CYP1A2 Inhibitor	Yes
	CYP2C19 Inhibitor	No
	CYP2C9 Inhibitor	No
	CYP2D6 Inhibitor	No
	CYP3A4 Inhibitor	No
	Log Kp (Skin Permeation)	-6.44 cm/s
Druglikeness	Lipinski	Yes; 0 violation
	Ghose	Yes
	Veber	Yes
	Egan	Yes
	Muegge	Yes
	Bioavailability Score	0.55
Medicinal Chemistry	PAINS	0 alert
	Brenk	0 alert
	Leadlikeness	Yes
	Synthetic Accessibility	3.01

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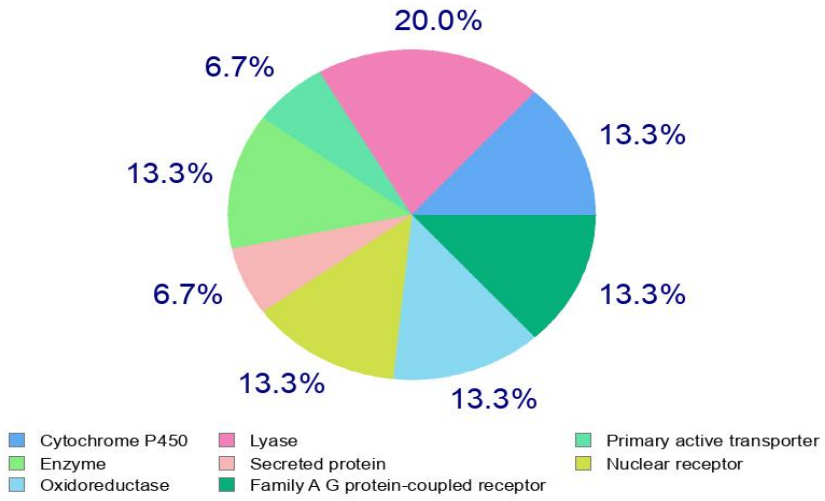

Fig 3: Targets of Naringenin

Table 3: Targets of Naringenin

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*
Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450	0.912946
Carbonic anhydrase VII	CA7	P43166	CHEMBL2326	Lyase	0.912946
Multidrug resistance-associated protein 1	ABCC1	P33527	CHEMBL3004	Primary active transporter	0.912946
Estradiol 17-beta-dehydrogenase 1	HSD17B1	P14061	CHEMBL3181	Enzyme	0.912946
Carbonic anhydrase XII	CA12	O43570	CHEMBL3242	Lyase	0.912946
Testis-specific androgen-binding protein	SHBG	P04278	CHEMBL3305	Secreted protein	0.912946
Carbonic anhydrase IV	CA4	P22748	CHEMBL3729	Lyase	0.912946
Cytochrome P450 1B1	CYP1B1	Q16678	CHEMBL4878	Cytochrome P450	0.912946
Carbonyl reductase [NADPH] 1	CBR1	P16152	CHEMBL5586	Enzyme	0.912946
Estrogen receptor alpha	ESR1	P03372	CHEMBL206	Nuclear receptor	0.583886
Estrogen receptor beta	ESR2	Q92731	CHEMBL242	Nuclear receptor	0.583886
Cyclooxygenase-1	PTGS1	P23219	CHEMBL221	Oxidoreductase	0.428281
Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase	0.362675
Adenosine A1 receptor	ADORA1	P30542	CHEMBL226	Family A G protein-coupled	0.166097

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				receptor	
Adenosine A3 receptor	ADORA3	P0DMS8	CHEMBL256	Family A G protein-coupled receptor	0.141522
ATP-binding cassette sub-family G member 2	ABCG2	Q9UNQ0	CHEMBL5393	Primary active transporter	0.125143
Taste receptor type 2 member 31	TAS2R31	P59538	CHEMBL2034804	Taste family G protein-coupled receptor	0.125143
Aldo-keto-reductase family 1 member C3	AKR1C3	P42330	CHEMBL4681	Enzyme	0.125143
Phospholipase A2 group 1B	PLA2G1B	P04054	CHEMBL4426	Enzyme	0.116965
Metabotropic glutamate receptor 5	GRM5	P41594	CHEMBL3227	Family C G protein-coupled receptor	0.116965
Acyl coenzyme A:cholesterol acyltransferase	CES1	P23141	CHEMBL2265	Enzyme	0.108771
Peroxisome proliferator-activated receptor gamma	PPARG	P37231	CHEMBL235	Nuclear receptor	0.108771
Carboxylesterase 2	CES2	O00748	CHEMBL3180	Enzyme	0.108771
Sodium/glucose cotransporter 2	SLC5A2	P31639	CHEMBL3884	Electrochemical transporter	0.100579
Matrix metalloproteinase 12	MMP12	P39900	CHEMBL4393	Protease	0.100579
DNA polymerase beta (by homology)	POLB	P06746	CHEMBL2392	Enzyme	0.100579
Matrix metalloproteinase 13	MMP13	P45452	CHEMBL280	Protease	0.100579
Phospholipase A2 group IIA	PLA2G2A	P14555	CHEMBL3474	Enzyme	0.100579
Phospholipase A2 group V	PLA2G5	P39877	CHEMBL4323	Enzyme	0.100579
Group X secretory phospholipase A2	PLA2G10	O15496	CHEMBL4342	Enzyme	0.100579
Beta-secretase 1	BACE1	P56817	CHEMBL4822	Protease	0.100579
Neuronal acetylcholine receptor protein alpha-7 subunit	CHRNA7	P36544	CHEMBL2492	Ligand-gated ion channel	0.100579
Kallikrein 1	KLK1	P06870	CHEMBL2319	Protease	0.100579
Kallikrein 2	KLK2	P20151	CHEMBL2442	Protease	0.100579
Retinoid X receptor alpha	RXRA	P19793	CHEMBL2061	Nuclear receptor	0.100579
Plasminogen activator inhibitor-1	SERPINE1	P05121	CHEMBL3475	Secreted protein	0.100579

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Tyrosine-protein kinase SRC	SRC	P12931	CHEMBL267	Kinase	0.100579
Carbonic anhydrase II	CA2	P00918	CHEMBL205	Lyase	0.100579
Carbonic anhydrase I	CA1	P00915	CHEMBL261	Lyase	0.100579
17-beta-hydroxysteroid dehydrogenase 14	HSD17B14	Q9BPX1	CHEMBL3712868	Enzyme	0.100579
Stem cell growth factor receptor	KIT	P10721	CHEMBL1936	Kinase	0.100579
Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase	0.100579
Fibroblast growth factor receptor 1	FGFR1	P11362	CHEMBL3650	Kinase	0.100579
Hepatocyte growth factor receptor	MET	P08581	CHEMBL3717	Kinase	0.100579
Carbonic anhydrase III	CA3	P07451	CHEMBL2885	Lyase	0.100579
Carbonic anhydrase VI	CA6	P23280	CHEMBL3025	Lyase	0.100579
Carbonic anhydrase XIII	CA13	Q8N1Q1	CHEMBL3912	Lyase	0.100579
Carbonic anhydrase VB	CA5B	Q9Y2D0	CHEMBL3969	Lyase	0.100579
Carbonic anhydrase VA	CA5A	P35218	CHEMBL4789	Lyase	0.100579
Quinone reductase 2	NQO2	P16083	CHEMBL3959	Enzyme	0.100579
Cathepsin (B and K)	CTSB	P07858	CHEMBL4072	Protease	0.100579
NADPH oxidase 4	NOX4	Q9NPH5	CHEMBL1250375	Enzyme	0.100579
Aldose reductase	AKR1B1	P15121	CHEMBL1900	Enzyme	0.100579
Dual specificty protein kinase CLK1	CLK1	P49759	CHEMBL4224	Kinase	0.100579
Dual specificity tyrosine-phosphorylation-regulated kinase 1B	DYRK1B	Q9Y463	CHEMBL5543	Kinase	0.100579
Butyrylcholinesterase	BCHE	P06276	CHEMBL1914	Hydrolase	0.100579
Carbonic anhydrase IX	CA9	Q16790	CHEMBL3594	Lyase	0.100579
Estrogen-related receptor alpha	ESRRA	P11474	CHEMBL3429	Nuclear receptor	0.100579
Estrogen-related receptor beta	ESRRB	O95718	CHEMBL3751	Nuclear receptor	0.100579
Cyclin-dependent kinase 5/CDK5 activator 1	CDK5R1 CDK5	Q15078 Q00535	CHEMBL1907600	Kinase	0.100579
Insulin-like growth factor I receptor	IGF1R	P08069	CHEMBL1957	Kinase	0.100579
Insulin receptor	INSR	P06213	CHEMBL1981	Kinase	0.100579
Dual-specificity tyrosine-phosphorylation regulated kinase 1A	DYRK1A	Q13627	CHEMBL2292	Kinase	0.100579
Estradiol 17-beta-	HSD17B2	P37059	CHEMBL2789	Enzyme	0.100579

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dehydrogenase 2					
Insulin-like growth factor binding protein 3	IGFBP3	P17936	CHEMBL3997	Secreted protein	0.100579
Matrix metalloproteinase 2	MMP2	P08253	CHEMBL333	Protease	0.100579
14-3-3 protein gamma	YWHAG	P61981	CHEMBL1293296	Unclassified protein	0.100579
NAD-dependent deacetylase sirtuin 2	SIRT2	Q8IXJ6	CHEMBL4462	Eraser	0.100579
Coagulation factor VII/tissue factor	F3	P13726	CHEMBL4081	Surface antigen	0.100579
Prostanoid EP1 receptor	PTGER1	P34995	CHEMBL1811	Family A G protein-coupled receptor	0.100579
Prostanoid EP2 receptor	PTGER2	P43116	CHEMBL1881	Family A G protein-coupled receptor	0.100579
Prostanoid EP3 receptor	PTGER3	P43115	CHEMBL3710	Family A G protein-coupled receptor	0.100579
Apoptosis regulator Bcl-X	BCL2L1	Q07817	CHEMBL4625	Other ion channel	0.100579
PI3-kinase p110-beta subunit	PIK3CB	P42338	CHEMBL3145	Enzyme	0.100579
Cytochrome P450 2C9	CYP2C9	P11712	CHEMBL3397	Cytochrome P450	0.100579
Cytochrome P450 3A4	CYP3A4	P08684	CHEMBL340	Cytochrome P450	0.100579
PI3-kinase p110-alpha subunit	PIK3CA	P42336	CHEMBL4005	Enzyme	0.100579
Transitional endoplasmic reticulum ATPase	VCP	P55072	CHEMBL1075145	Primary active transporter	0.100579
Placenta growth factor	PGF	P49763	CHEMBL1697671	Unclassified protein	0.100579
Vascular endothelial growth factor A	VEGFA	P15692	CHEMBL1783	Secreted protein	0.100579
Endothelin receptor ET-A	EDNRA	P25101	CHEMBL252	Family A G protein-coupled receptor	0.100579
Serine/threonine-protein kinase/endoribonuclease IRE1	ERN1	O75460	CHEMBL1163101	Enzyme	0.100579
Matrix metalloproteinase 3	MMP3	P08254	CHEMBL283	Protease	0.100579
Beta amyloid A4 protein	APP	P05067	CHEMBL2487	Membrane receptor	0.100579
Glycogen synthase kinase-	GSK3B	P49841	CHEMBL262	Kinase	0.100579

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3 beta					
Apoptosis regulator Bcl-2	BCL2	P10415	CHEMBL4860	Other ion channel	0.100579
Matrix metalloproteinase 9	MMP9	P14780	CHEMBL321	Protease	0.100579
Serine/threonine-protein kinase WEE1	WEE1	P30291	CHEMBL5491	Kinase	0.100579
Tyrosine-protein kinase LCK	LCK	P06239	CHEMBL258	Kinase	0.100579
Tyrosine-protein kinase SYK	SYK	P43405	CHEMBL2599	Kinase	0.100579
Cyclin-dependent kinase 2/cyclin E1	CCNE1 CDK2	P24864 P24941	CHEMBL1907605	Kinase	0.100579
CDK3/Cyclin E	CCNE1 CDK3	P24864 Q00526	CHEMBL3038471	Kinase	0.100579
Cyclin-dependent kinase 4	CDK4	P11802	CHEMBL331	Kinase	0.100579
Serine/threonine-protein kinase Aurora-A	AURKA	O14965	CHEMBL4722	Kinase	0.100579
Alpha-synuclein	SNCA	P37840	CHEMBL6152	Unclassified protein	0.100579
Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687	Enzyme	0.100579
Hepatocyte nuclear factor 4-alpha	HNF4A	P41235	CHEMBL5398	Unclassified protein	0.100579

Table 4: Common Targets Between Psoriasis and Naringenin

Targets Disease	Compound	Common Targets
Psoriasis	Naringenin	VEGFA, PPARG, MMP9, MMP2, BCL2L1, KDR, ALOX12, PGF, BCL2, ABCG2, PTGS1, MMP3, RXRA, SERPINE1, VCP, MMP13, CYP1B1, CDK4, AURKA, CTSB, IGF1R, AKR1C3, GSK3B, PLA2G2A, ABCC1, IGFBP3, MMP12, SYK, ESR1, CYP3A4, CYP2C9, CHRNA7, EDNRA, ADORA3, SHBG, APP, PIK3CB, NOX4, SRC, KLK1, KIT, KLK2, HNF4A, PIK3CA, ESR2, ERN1, ESRRA, PLA2G5, CA9, PTGER3, FGFR1, CA2, BACE1, PTGER2, WEE1, LCK, CA3, SLC5A2, CES2, PTGER1

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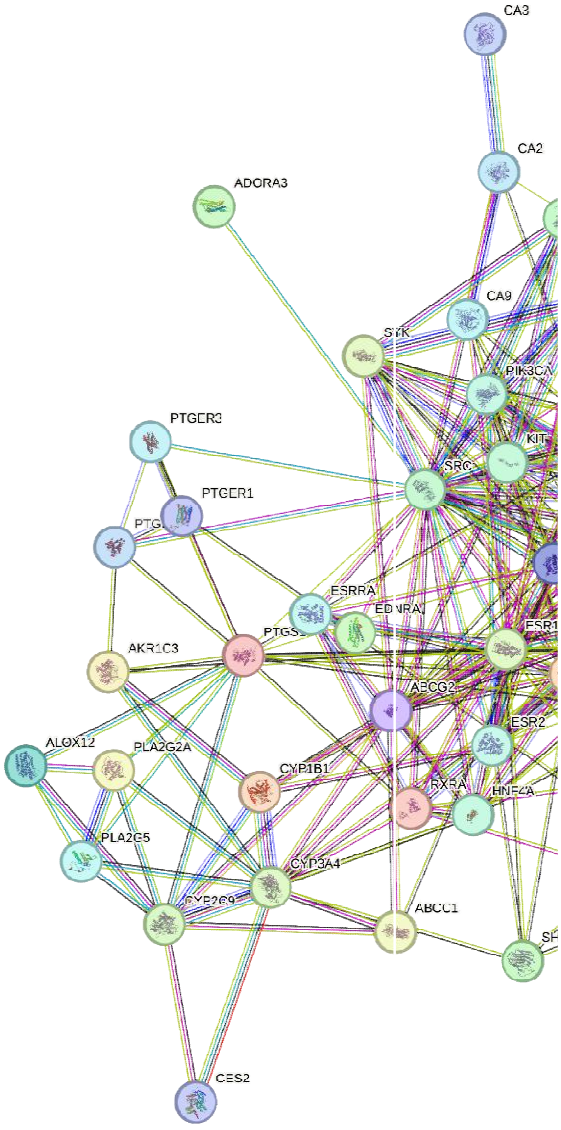

Fig 4: Protein-protein interactions (PPIs)

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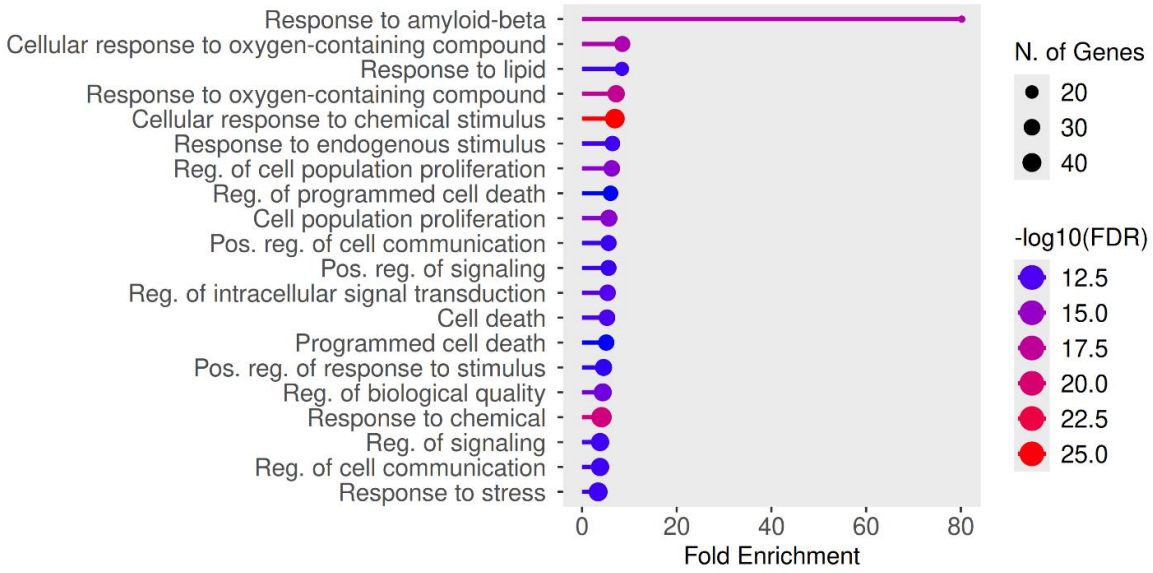

Fig 5: GO biological process

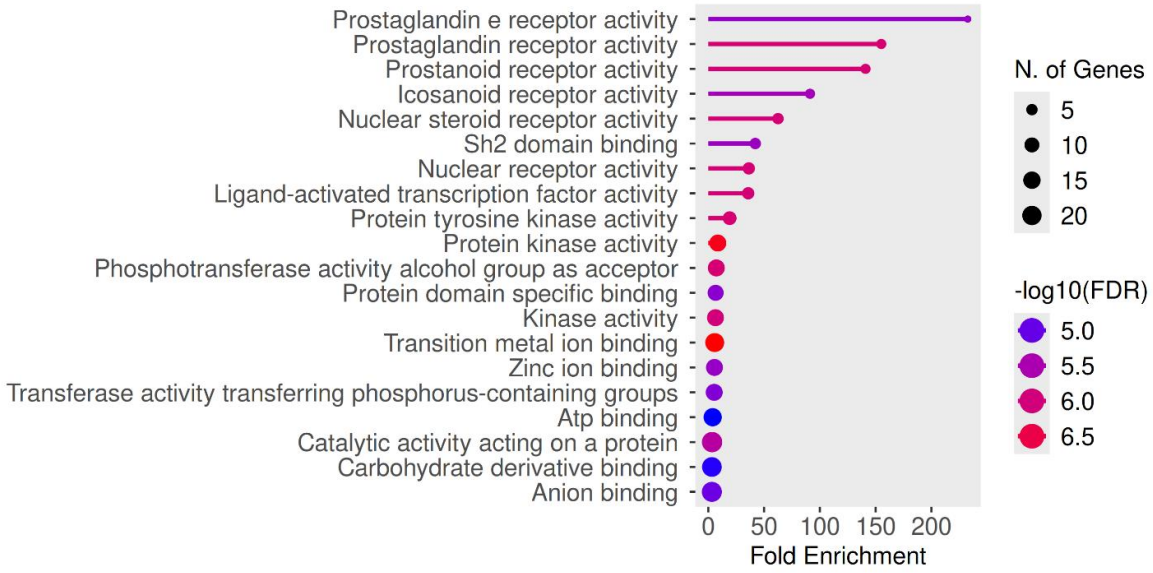

Fig 6: Go cellular component

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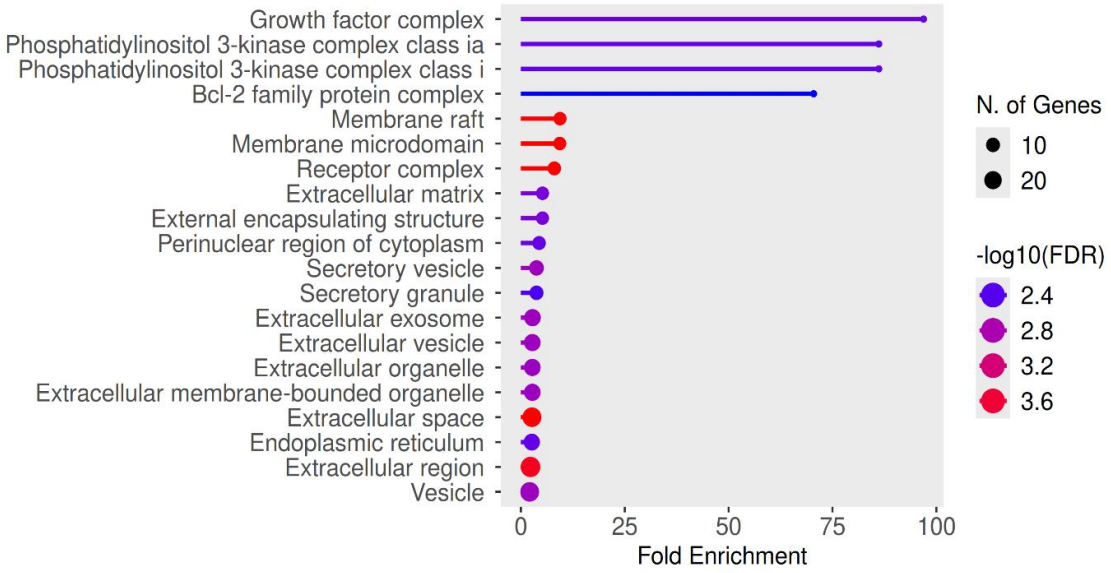

Fig 7: GO molecular function

Table 5: **Top 5 Key Targets in Psoriasis–Naringenin Network**

Target	Full Name	Role in Psoriasis	Importance of Naringenin Interaction
VEGFA	Vascular Endothelial Growth Factor A	Promotes angiogenesis, inflammation, and keratinocyte proliferation in psoriatic lesions	Naringenin may reduce abnormal blood vessel formation and inflammation
PPARG	Peroxisome Proliferator-Activated Receptor Gamma	Regulates inflammation, lipid metabolism, and skin cell differentiation	Activation helps suppress inflammatory cytokines and improves skin barrier function
MMP9	Matrix Metalloproteinase-9	Causes extracellular matrix degradation and inflammatory tissue remodeling	Naringenin may inhibit tissue damage and inflammatory infiltration
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-Kinase Catalytic Subunit Alpha	Central component of PI3K/AKT signaling involved in keratinocyte hyperproliferation	Modulation may reduce abnormal cell growth and immune activation
SRC	Proto-oncogene Tyrosine-Protein Kinase Src	Involved in inflammatory signaling and immune cell activation	Naringenin may suppress downstream inflammatory pathways

Discussion of Results

The present network pharmacology study explored the therapeutic potential of Naringenin against psoriasis through a multi-target and multi-pathway approach. Psoriasis is a chronic immune-mediated inflammatory skin disorder characterized by excessive keratinocyte proliferation, inflammatory cytokine release, angiogenesis, and immune dysregulation. The findings of this study suggest that Naringenin may exert anti-psoriatic effects through the modulation of several molecular targets and signaling pathways associated with disease progression.

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The physicochemical and pharmacokinetic analysis demonstrated that Naringenin possesses favorable drug-like properties. The compound satisfied Lipinski's rule of five without violations, indicating good oral bioavailability and pharmacological suitability. The consensus Log P value of 1.91 suggested moderate lipophilicity, which may facilitate membrane permeability and cellular uptake. Furthermore, the high gastrointestinal absorption and absence of major medicinal chemistry alerts support the potential therapeutic applicability of Naringenin.

Target prediction analysis identified multiple proteins associated with inflammation, oxidative stress, angiogenesis, and immune regulation. Among these, several targets overlapped with psoriasis-associated genes, indicating a strong pharmacological relationship between Naringenin and psoriasis pathology. The common targets included VEGFA, PPARG, MMP9, MMP2, BCL2L1, KDR, PTGS1, SRC, PIK3CA, SYK, NOX4, and others, suggesting that Naringenin acts through a polypharmacological mechanism rather than a single-target effect.

The compound–target–disease network analysis revealed extensive interactions between Naringenin and psoriasis-related proteins. The high connectivity of hub targets indicated their important regulatory role in disease progression. Network topology analysis highlighted VEGFA, PPARG, MMP9, PIK3CA, and SRC as major hub genes, suggesting that these proteins may serve as critical therapeutic mediators.

VEGFA emerged as one of the most significant targets in the network. VEGFA plays an essential role in angiogenesis and vascular permeability in psoriatic lesions. Increased VEGFA expression contributes to abnormal blood vessel formation, inflammatory cell infiltration, and epidermal hyperplasia. Naringenin interaction with VEGFA suggests its potential to suppress angiogenesis and reduce inflammation within psoriatic plaques. This finding is supported by previous studies reporting the anti-angiogenic activity of flavonoids in inflammatory disorders.

PPARG was another major target identified in the study. PPARG is a nuclear receptor involved in lipid metabolism, keratinocyte differentiation, and inflammatory regulation. Reduced PPARG activity has been associated with enhanced inflammatory cytokine production in psoriasis. Activation or modulation of PPARG by Naringenin may help restore epidermal homeostasis and suppress inflammatory responses by inhibiting cytokines such as TNF-α, IL-6, and IL-17.

Matrix metalloproteinases, particularly MMP9 and MMP2, were strongly represented among the overlapping targets. MMPs are involved in extracellular matrix degradation and tissue remodeling during chronic inflammation. Overexpression of MMP9 in psoriasis contributes to keratinocyte migration, inflammatory infiltration, and tissue damage. The ability of Naringenin to interact with MMP9 and MMP2 suggests that it may reduce pathological tissue remodeling and inflammatory progression in psoriatic skin.

The identification of PIK3CA and SRC further indicated the involvement of intracellular signaling pathways associated with keratinocyte proliferation and immune activation. The PI3K/AKT signaling pathway regulates cell survival, proliferation, and inflammatory responses in psoriasis. Abnormal activation of this pathway promotes epidermal hyperplasia and chronic inflammation. Naringenin-mediated modulation of PIK3CA may therefore reduce keratinocyte overproliferation and immune dysregulation. Similarly, SRC kinase plays a major role in inflammatory signaling cascades and immune cell activation, and its inhibition may contribute to anti-inflammatory effects.

Additional targets such as NOX4, PTGS1, SYK, PLA2G2A, and ALOX12 also indicate the antioxidant and anti-inflammatory potential of Naringenin. NOX4 contributes to reactive oxygen species generation and oxidative stress in inflamed tissues, whereas PTGS1 and phospholipase-related enzymes participate in prostaglandin and leukotriene synthesis. Modulation of these targets suggests that Naringenin may reduce oxidative damage and inflammatory mediator production in psoriasis.

GO enrichment analysis demonstrated that the common targets were mainly involved in biological processes such as inflammatory response, regulation of apoptosis, angiogenesis, protein phosphorylation, immune response, and cell proliferation. Cellular component analysis revealed enrichment in membrane regions, cytoplasm, extracellular space, and receptor complexes, whereas molecular function analysis indicated kinase activity, enzyme binding, receptor binding, and protein kinase activity. These findings collectively support the multi-target regulatory mechanism of Naringenin.

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KEGG pathway analysis further demonstrated significant enrichment in pathways associated with psoriasis pathogenesis, including PI3K-Akt signaling pathway, MAPK signaling pathway, VEGF signaling pathway, inflammatory mediator regulation, apoptosis pathways, and cytokine-related signaling pathways. These pathways are known to regulate keratinocyte proliferation, angiogenesis, oxidative stress, and inflammatory cytokine production in psoriasis. The enrichment results strongly suggest that Naringenin may exert therapeutic effects through simultaneous modulation of interconnected signaling networks.

Overall, the present findings indicate that Naringenin possesses considerable therapeutic potential against psoriasis through its anti-inflammatory, antioxidant, anti-proliferative, and immunomodulatory properties. The network pharmacology approach successfully revealed the complex interactions between Naringenin and psoriasis-associated molecular targets. However, the present study is primarily based on computational predictions and database analyses. Therefore, further in vitro, in vivo, and clinical studies are necessary to validate the identified targets and signaling pathways and to confirm the therapeutic efficacy of Naringenin in psoriasis management.

CONCLUSION

The present network pharmacology study demonstrated that Naringenin possesses significant therapeutic potential against psoriasis through a multi-target and multi-pathway mechanism of action. The analysis identified several important overlapping targets between Naringenin and psoriasis, including VEGFA, PPARG, MMP9, PIK3CA, and SRC, which are closely associated with inflammation, angiogenesis, immune regulation, oxidative stress, and keratinocyte hyperproliferation. GO and KEGG enrichment analyses further revealed that Naringenin may regulate multiple signaling pathways such as PI3K-Akt, MAPK, VEGF, and inflammatory mediator pathways involved in psoriasis pathogenesis. The favorable pharmacokinetic and drug-likeness properties of Naringenin additionally support its potential as a bioactive therapeutic compound. Overall, the findings indicate that Naringenin may serve as a promising natural agent for psoriasis treatment by modulating complex molecular networks associated with disease progression. However, further in vitro, in vivo, and clinical studies are required to validate these computational findings and establish its therapeutic efficacy and safety in psoriasis management.

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