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Research Paper

Multi-Target Therapeutic Potential of Psoralen and Diosgenin against Psoriasis via Network Pharmacology

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Abstract
Psoriasis is a chronic immune-mediated inflammatory skin condition marked by keratinocyte hyperproliferation, immunological dysregulation, and oxidative stress, profoundly impacting patients' quality of life. Existing therapy modalities, including topical medicines, systemic medications, and biologics, encounter constraints including unpleasant effects, elevated costs, and suboptimal therapeutic results. Natural substances exhibiting multi-target pharmacological characteristics provide a viable option for the therapy of psoriasis. This research utilizes a network pharmacology method to extensively examine the therapeutic potential and mechanisms of Psoralen and Diosgenin in regulating pathways linked with psoriasis. Genes associated with psoriasis were extracted from several databases, and a robust protein–protein interaction (PPI) network was established, highlighting critical hub proteins including IL6, TNF, PTGS2, and STAT3. Analysis of compound–target interactions revealed that Psoralen mostly targets superoxide dismutase 1 (SOD1), which is crucial for antioxidant defense, while Diosgenin engages with many targets, including MAPK8, TNF, and PTGS2, that are implicated in inflammatory and immunological signaling pathways. Gene Ontology (GO) and illness enrichment analysis corroborated the significant correlation of these targets with psoriasis vulgaris, psoriatic arthritis, and other immune-inflammatory conditions.ADME assessment using the SwissADME methodology revealed advantageous pharmacokinetic characteristics for both substances, including increased gastrointestinal absorption, blood-brain barrier permeability, and drug-likeness. The integrated network analysis elucidates the synergistic processes of Psoralen and Diosgenin, whereby their antioxidant and anti-inflammatory properties together address psoriasis pathogenesis. This multi-target approach highlights their promise as viable therapeutic options, prompting more experimental validation and clinical research. The research highlights the significance of network pharmacology in facilitating the identification of innovative multi-target therapies for intricate illnesses like psoriasis.

Keywords: *Network Pharmacology, Psoriasis, Psoralen, Diosgenin, Protein–Protein Interaction (PPI) Network*

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I. Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin condition that affects roughly 2–3% of the worldwide population, significantly impacting physical, psychological, and social well-being. The condition is characterized by erythematous, scaly plaques mostly located on the elbows, knees, scalp, and lower back, defined by hyperproliferation of keratinocytes, immune cell infiltration, and excessive secretion of pro-inflammatory cytokines [1]. Psoriasis presents in several clinical manifestations, including psoriasis vulgaris (the most prevalent), pustular psoriasis, and psoriatic arthritis, each indicating differing levels of systemic involvement. Despite advancements in comprehending the pathophysiology of psoriasis, its precise etiology remains complex, including genetic, immunological, and environmental variables that facilitate disease onset and advancement[2,3].

Psoriasis is molecularly induced by immune system dysregulation, namely involving the IL-23/IL-17 axis, which facilitates the generation of inflammatory cytokines and the proliferation of keratinocytes. Crucial cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and interleukin-17A (IL-17A), facilitate a pro-inflammatory milieu in the skin, resulting in chronic inflammation, heightened oxidative stress, and epidermal hyperplasia. The interaction between keratinocytes and immune cells, especially T-helper 17 (Th17) cells, sustains the inflammatory feedback loop, worsening psoriatic lesions. Furthermore, oxidative stress, marked by the overproduction of reactive oxygen species (ROS), leads to keratinocyte injury, the expression of inflammatory genes, and the activation of immune cells, playing a crucial role in disease pathogenesis[4,5].

Current treatment modalities for psoriasis include topical medicines (corticosteroids, vitamin D analogs), systemic medications (methotrexate, cyclosporine), and biologics that target TNF, IL-12/IL-23, and IL-17 pathways. Although these therapies may proficiently alleviate symptoms, they are linked to constraints including systemic toxicity, elevated costs, the development of drug resistance, and partial remission in some patient demographics[6]. Biologics, despite their excellent specificity, often result in immunosuppression and an elevated risk of infection. Furthermore, single-target therapy may inadequately address the multifactorial characteristics of psoriasis, which include several redundant and compensatory mechanisms. This underscores the need for innovative, safe, and multi-targeted treatment strategies capable of more effectively modulating the intricate pathophysiology of psoriasis[7,8].

Natural chemicals have surfaced as intriguing options owing to their extensive pharmacological profiles, little toxicity, and multi-target processes. Psoralen and Diosgenin are notable for their established anti-inflammatory, antioxidant, and immunomodulatory characteristics, which are significantly pertinent to the pathophysiology of psoriasis[9,10]. Psoralen, a furanocoumarin extracted from Psoraleacorylifolia, has historically been used in traditional medicine for dermatological conditions, especially in conjunction with phototherapy. Its antioxidant properties allow it to neutralize free radicals, diminish oxidative damage, and suppress inflammatory gene expression. Diosgenin, a steroidal saponin present in Dioscorea species, is recognized for its ability to modulate immunological responses, diminish inflammatory cytokine levels, and safeguard against oxidative stress-induced damage[11,12]. Notwithstanding these encouraging characteristics, the specific molecular targets and interaction networks of these drugs in relation to psoriasis are yet inadequately defined[13].

Network pharmacology provides a robust, systems-oriented methodology to analyze the multi-target interactions of bioactive chemicals in complex illnesses like psoriasis. In contrast to conventional one-drug-one-target models, network pharmacology acknowledges the polygenic characteristics of illnesses and the ability of certain compounds to concurrently influence numerous targets[14–16]. Network pharmacology facilitates the mapping of complex interaction networks and identifies possible treatment hubs by combining data from gene-disease connections, protein-protein interaction networks, gene ontology (GO), and compound-target prediction databases. This method enables a thorough comprehension of disease processes and chemical interactions, uncovering new treatment candidates and repurposing current drugs for intricate illnesses[17].

This research used a network pharmacology framework to examine the possible therapeutic effects of Psoralen and Diosgenin on psoriasis. We methodically identified genes associated with psoriasis from various databases, developed a robust protein–protein interaction (PPI) network to elucidate hub proteins and functional interactions, and conducted compound–target interaction mapping to forecast direct targets of Psoralen and Diosgenin within the psoriasis network[18]. Additionally, gene ontology and illness enrichment studies were performed to elucidate the functional significance of target genes and their correlation with psoriasis and associated immune-inflammatory conditions.

An ADME (Absorption, Distribution, Metabolism, and Excretion) analysis was conducted utilizing the SwissADME tool to evaluate the drug-likeness and pharmacokinetic appropriateness of these compounds, offering insights into their potential bioavailability, blood-brain barrier permeability, and interactions with cellular transporters. The BOILED-Egg model was used to illustrate gastrointestinal absorption and blood-brain barrier permeability, essential factors for systemic medicinal efficacy[19].

Our research indicates that Psoralen primarily targets superoxide dismutase 1 (SOD1), an essential enzyme in reactive oxygen species detoxification, suggesting its main function in alleviating oxidative stress in psoriatic lesions. Diosgenin exhibits a multi-target profile, engaging with mitogen-activated protein kinase 8 (MAPK8), tumor necrosis factor (TNF), and prostaglandin-endoperoxide synthase 2 (PTGS2), indicating its capacity to influence inflammatory signaling, cytokine expression, and prostaglandin synthesis[20].

The integrated research highlights the complimentary and possibly synergistic functions of Psoralen and Diosgenin in targeting the fundamental pathogenic factors of psoriasis: oxidative stress and chronic inflammation. This dual-target technique presents a potential therapeutic avenue, necessitating more experimental validation and clinical assessment to establish effective and safe multi-target therapies for psoriasis[21].

II. Materials and Methods

Data Collection of Psoriasis-Associated Genes

A systematic search was performed across several databases (GeneCards, DisGeNET, swissADME) to find genes linked with psoriasis. The selection process included relevance score thresholds and validation of literature. Fifteen pivotal genes were selected for further analysis: IL23R, TYK2, IL12B, S100A7, NOS2, IL36G, IL6, TNF, IL1B, IL17A, CXCL8, STAT3, CCL20, JAK2, and PTGS2.

Table 1: Selected genes for psoriasis from different databases

Gene Symbol	Gene Name (Full)	UniProt ID
IL23R	Interleukin-23 receptor	Q5VWK5
TYK2	Tyrosine-protein kinase TYK2	P29597
IL12B	Interleukin-12 subunit beta	P29460
S100A7	Protein S100-A7	P31151
NOS2	Nitric oxide synthase, inducible	P35228
IL36G	Interleukin-36 gamma	Q9NZH8
IL6	Interleukin-6	P05231
TNF	Tumor necrosis factor	P01375
IL1B	Interleukin-1 beta	P01584
IL17A	Interleukin-17A	Q16552
CXCL8	Interleukin-8 (C-X-C motif chemokine ligand 8)	P10145
STAT3	Signal transducer and activator of transcription 3	P40763
CCL20	C-C motif chemokine ligand 20	P78556
JAK2	Tyrosine-protein kinase JAK2	O60674
PTGS2	Prostaglandin G/H synthase 2 (Cyclooxygenase-2)	P35354

Protein–Protein Interaction (PPI) Network Construction

The STRING database (https://string-db.org) was used to develop the PPI network of chosen psoriasis-related genes. The threshold for the interaction confidence score was established at 0.7, indicating strong confidence. The resultant network was displayed with Cytoscape 3.10.3, and hub proteins were determined based on node degree centrality, betweenness, and proximity[22].

Compound Target Prediction

The PubChem database provided the chemical structures of Diosgenin (PubChem CID: 99474) and Psoralen (PubChem CID: 5280665). The SwissTargetPrediction and STITCH databases were used to forecast possible protein targets for both drugs. The targets were compared with psoriasis-associated genes to detect overlapping targets[23].

Compound–Target Network Construction

A compound-target interaction network was created with Cytoscape. Nodes signify chemicals and target proteins, while edges indicate anticipated interactions. Key target proteins exhibiting significant connectivity were examined for their involvement in psoriasis pathways[23].

Gene Ontology (GO) and Disease Enrichment Analysis

Gene Ontology analysis (biological processes, molecular functions, and cellular components) was conducted using DAVID (https://david.ncifcrf.gov) and Metascape (https://metascape.org). Astudy of disease association was performed to assess the statistical significance of the involvement of target genes in psoriasis and associated illnesses. Enrichment was shown as bar graphs displaying –log10 (P) values[23].

ADME Analysis

The SwissADME online tool (http://www.swissadme.ch) was used to assess the pharmacokinetic characteristics of Psoralen and Diosgenin, encompassing lipophilicity, molecular weight, topological polar surface area (TPSA), gastrointestinal absorption, blood-brain barrier penetration, and drug-likeness. The BOILED-Egg model was used to forecast blood-brain barrier and gastrointestinal absorption capabilities[24].

Statistical Analysis

All in silico studies used standard database criteria and configurations. This research does not include any experimental biological validation. Network metrics were computed using the integrated facilities of Cytoscape. The significance in illness enrichment was determined by $P < 0.05$.

III. Results

Network Pharmacology Results

Protein–Proteininteraction(PPI)networkforPsoriasis

The protein–protein interaction (PPI) network analysis elucidates the intricate relationships among psoriasis-related targets, offering a comprehensive picture of their connectivity and functional importance[25]. The network is circular and has several nodes, each symbolizing a protein, interconnected by differently colored edges that denote functional relationships and biological significance. The research indicates that the network is extensively linked, implying collaborative processes among cytokines, enzymes, transcription factors, and signaling molecules that play a role in psoriasis pathogenesis[26].Fifteen protein nodes were found in this PPI network: IL23R, TYK2, IL12B, S100A7, NOS2, IL36G, IL6, TNF, IL1B, IL17A, CXCL8, STAT3, CCL20, JAK2, and PTGS2. The nodes are interconnected by a complex network of edges, signifying protein–protein interactions. The network has over 40 discernible edges, indicating a substantial interaction density. Certain nodes, such as IL6, TNF, PTGS2, and STAT3, emerge as hub proteins owing to their heightened interconnectedness, indicating their potential role as major regulators in psoriasis-related signaling cascades[27].

IL6 has a pivotal role within the network, with several connections to TNF, IL1B, IL17A, STAT3, and PTGS2. This importance underscores IL6 as a pivotal cytokine coordinating inflammatory pathways. Likewise, TNF has several associations, underscoring its function as a principal inflammatory cytokine in psoriasis. PTGS2 (COX-2) interacts with many proteins, including JAK2, IL6, TNF, and IL1B, indicating its role in the manufacture of inflammatory prostaglandins associated with immunological activation. STAT3 has numerous connections, underscoring its significance as a transcription factor governing cytokine-induced keratinocyte hyperproliferation[28].

Additional significant nodes are IL23R and TYK2, both associated with IL12B and IL17A. These links indicate the activation of the IL-23/IL-17 axis, a recognized pathogenic mechanism in psoriasis. IL12B, along with TYK2 and IL23R, indicates its involvement in facilitating Th1/Th17-mediated immune responses. IL17A and CXCL8 (IL8) exhibit significant connection, associating immunological signaling with neutrophil recruitment and persistent inflammation. IL36G contributes to the inflammatory complexity by interacting with other cytokines. NOS2 and S100A7 have a role in oxidative stress and the modulation of antimicrobial peptides, both of which are crucial in psoriatic lesions[29].

The network suggests that these proteins do not function independently but instead create a collaborative signaling framework that enhances inflammation and immunological responses. The intricate linkages indicate redundancy and resilience within the system, since several pathways converge on common targets including TNF, IL6, and STAT3. These hub proteins may represent prospective targets for therapeutic intervention, since their inhibition might concurrently impair several downstream inflammatory pathways.

The PPI network has 15 nodes and around 40 edges, with IL6, TNF, PTGS2, and STAT3 serving as key hubs. The robust interconnection emphasizes the multi-faceted character of psoriasis pathogenesis and reinforces the need of coordinated therapy approaches designed to concurrently modulate many pathways. This systems-level knowledge from network pharmacology enhances the comprehension of disease biology and facilitates drug development strategies aimed at hub proteins[16,30].

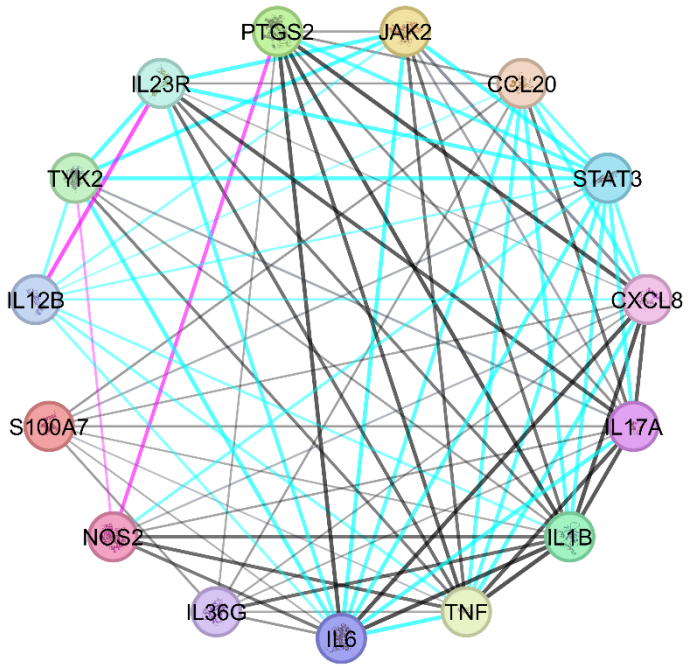

Figure 1: Protein–protein interaction (PPI) network of psoriasis-associated targets illustrating 15 interconnected nodes and more than 40 edges, with IL6, TNF, PTGS2, and STAT3 emerging as hub proteins. The dense connectivity highlights the IL-23/IL-17 axis, cytokine signaling, oxidative stress, and inflammatory mediators, emphasizing the multi-target regulatory complexity in psoriasis pathogenesis.

The table below summarizes the genes and abbreviations involved in this network:

Gene/Protein	Abbreviation	Role in Psoriasis Pathways
Interleukin 23 Receptor	IL23R	Mediates IL-23 signaling, activates Th17 cells.
Tyrosine Kinase 2	TYK2	Key mediator of cytokine signaling, JAK-STAT pathway.
Interleukin 12 Subunit Beta	IL12B	Promotes Th1 and Th17 differentiation.
S100 Calcium-Binding Protein A7	S100A7	Antimicrobial peptide, linked to keratinocyte proliferation.
Nitric Oxide Synthase 2	NOS2	Produces nitric oxide, contributes to oxidative stress.
Interleukin 36 Gamma	IL36G	Amplifies inflammatory signaling in keratinocytes.
Interleukin 6	IL6	Central cytokine driving inflammation and immune response.
Tumor Necrosis Factor	TNF	Master pro-inflammatory cytokine central to psoriasis.
Interleukin 1 Beta	IL1B	Promotes inflammatory responses and cytokine cascades.
Interleukin 17A	IL17A	Key effector cytokine in Th17 axis, neutrophil recruitment.
C-X-C Motif Chemokine Ligand 8	CXCL8	Recruits neutrophils, promotes inflammation.
Signal Transducer and Activator of Transcription 3	STAT3	Transcription factor driving cytokine-mediated proliferation.
C-C Motif Chemokine Ligand 20	CCL20	Involved in immune cell migration and inflammation.
Janus Kinase 2	JAK2	Mediator of cytokine receptor signaling via JAK-STAT.
Prostaglandin-Endoperoxide Synthase 2	PTGS2 (COX-2)	Inducible enzyme driving prostaglandin synthesis and inflammation.

Active metabolites target genes network

The network pharmacology study of Psoralen and Diosgenin demonstrated their interaction with many psoriasis-related protein targets, underscoring their potential involvement in regulating inflammatory and oxidative stress pathways. The shown network depicts the interactions between compounds and targets, with each drug linked to its corresponding protein targets by edges, signifying mechanistic connections and biological significance[31]. The illustration consists of two sections: Psoralen interacting with SOD1, and Diosgenin interacting with MAPK8, TNF, and PTGS2. Collectively, these networks underscore the multi-target pharmacological effects of the bioactive substances[32].

Psoralen was shown to interact directly with the SOD1 protein. Superoxide dismutase 1 (SOD1) is an essential enzyme in the defense mechanism against oxidative stress, facilitating the dismutation of superoxide radicals into hydrogen peroxide and oxygen. By targeting SOD1, Psoralen may modulate reactive oxygen species (ROS) levels in psoriatic circumstances, so minimizing excessive oxidative damage, a characteristic of chronic inflammation and skin lesions. The interaction between psoralen and SOD1 consists of one node (SOD1) linked to psoralen by a single edge, constituting a one-to-one interaction. This suggests that psoralen's main mechanistic role in this network may pertain to redox equilibrium and safeguarding against oxidative stress[33].

Diosgenin exhibited a more extensive interaction profile with three target proteins: MAPK8, TNF, and PTGS2. Mitogen-activated protein kinase 8 (MAPK8), often referred to as JNK1, is crucial in the modulation of apoptosis, inflammatory signaling, and stress responses. The interaction with Diosgenin indicates regulation of the MAPK signaling cascade, which is significantly pertinent to keratinocyte hyperproliferation and inflammatory cytokine generation in psoriasis[34]. Tumor necrosis factor (TNF) is a principal pro-inflammatory cytokine that orchestrates immunological responses and inflammation in the pathogenesis of psoriasis. The combination of diosgenin with TNF suggests a direct anti-inflammatory function, perhaps mitigating cytokine storms and immune-mediated dermal injury. Prostaglandin-endoperoxide synthase 2 (PTGS2), often referred to as COX-2, is an inducible enzyme involved in the manufacture of prostaglandins, which play a role in inflammation, pain, and immunological regulation. Diosgenin may decrease prostaglandin-mediated inflammation by targeting PTGS2, therefore offering symptomatic alleviation and disease management[35].

The Diosgenin network has a single chemical node linked to three protein nodes (MAPK8, TNF, and PTGS2), establishing three direct edges. Furthermore, the internal communication among the protein nodes enhances the network. TNF interacts with MAPK8 and PTGS2, indicating their collaborative role in inflammatory processes. This interconnectivity leads to a more cohesive subnetwork, whereby Diosgenin concurrently affects several signaling pathways. Diosgenin has a greater level of interaction than Psoralen, with three direct connections to its targets and a minimum of two supplementary protein–protein interaction edges inside the network.This indicates diosgenin's extensive and integrative pharmacological function in the control of psoriasis pathways[36].

The network analysis indicated that Psoralen interacts with one target protein (one edge), whereas Diosgenin interacts with three proteins (three edges), resulting in a total of four compound–target interactions. Incorporating protein–protein interactions among diosgenin's targets results in a network of six edges. The network consists of five protein nodes (SOD1, MAPK8, TNF, PTGS2) and two compound nodes (Psoralen and Diosgenin), with 6 to 7 significant edges, therefore creating a compound-target protein interaction map. This underscores the polypharmacological characteristics of natural compounds, with Diosgenin exhibiting a broader interaction range than Psoralen[37].

The results demonstrate that Psoralen mostly operates via antioxidant pathways by influencing SOD1, whereas Diosgenin has multi-target effects, regulating inflammation and immunological responses via MAPK8, TNF, and PTGS2. The variations in interaction patterns indicate parallel pharmacological effects, with Psoralen mitigating oxidative stress and Diosgenin reducing inflammatory mediators. This combination may significantly enhance psoriasis therapy, since oxidative imbalance and persistent inflammation are key pathogenic factors[23]. The integrated network highlights that natural chemicals such as Psoralen and Diosgenin are characterized by multi-target interactions rather than being confined to single-target pharmacology, hence underscoring their potential as therapeutic candidates. This comprehensive view emphasizes their ability to regulate interrelated biological processes, such as oxidative stress, cytokine signaling, and inflammatory pathways[38].

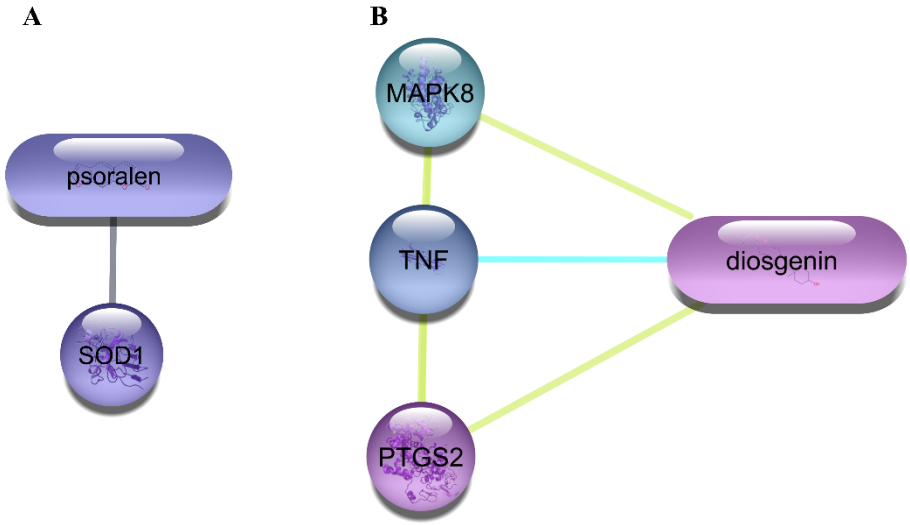

Figure 2: Network pharmacology-based compound–target interaction map showing Psoralen linked with SOD1 and Diosgenin associated with MAPK8, TNF, and PTGS2, highlighting their multi-target roles in oxidative stress and inflammation.

The detailed table below summarizes the genes, their abbreviations, and interaction with Psoralen and Diosgenin:

Compound	Target Protein	Abbreviation	Function in Psoriasis Pathways
Psoralen	Superoxide dismutase 1	SOD1	Antioxidant defense; reduces oxidative stress by converting superoxide radicals to hydrogen peroxide.
Diosgenin	Mitogen-activated protein kinase 8	MAPK8	Regulates apoptosis, inflammatory signaling, and keratinocyte stress responses.
Diosgenin	Tumor necrosis factor	TNF	Master pro-inflammatory cytokine driving immune-mediated psoriasis pathogenesis.
Diosgenin	Prostaglandin-endoperoxide synthase 2	PTGS2	Inducible enzyme (COX-2); promotes prostaglandin synthesis linked to inflammation and pain.

The research suggests that the interactions between Psoralen SOD1 and Diosgenin MAPK8/TNF/PTGS2 constitute a complimentary pharmacological network, whereby both medications target distinct but convergent pathogenic pathways associated with psoriasis. This dual targeting approach indicates potential therapeutic synergy, making them excellent candidates for future drug development and clinical validation[39].

Gene Ontology (GO) assessment

The gene ontology (GO) and disease association analysis shown in the bar graph underscores the substantial enrichment of targets linked with Psoralen and Diosgenin in psoriasis and similar inflammatory conditions. The x-axis of the graph denotes the -log10 (P) values, indicating the statistical significance of enrichment, whilst the y-axis enumerates the illness conditions. Psoriasis vulgaris had the strongest correlation with target genes, underscoring the significant relevance of the discovered targets to this illness. Psoriatic arthritis, pustulosis of the palms and soles, and periodontitis emerged as notably enhanced disorders. Additional significant relationships included generalized pustular psoriasis, chronic small plaque psoriasis, and dermatitis, confirming the pivotal role of immune dysregulation and persistent inflammation within the illness spectrum[17,40].

Psoriasis vulgaris had the greatest enrichment, with a -log10 (P) score over 30, indicating a substantial overlap of target genes with the molecular pathways associated with this illness. Psoriatic arthritis had a significant correlation, indicating the systemic engagement of inflammatory mediators beyond dermatological conditions. Other subtypes of psoriasis, such as generalized pustular psoriasis and chronic small plaque psoriasis, underscore the common biological foundations across many clinical variations[41]. Dermatologic diseases, including dermatitis and inflammatory dermatosis, were considerably enriched, indicating shared molecular targets related to immune-inflammatory pathways. In addition to dermatology, systemic ailments such as Behcet syndrome, ankylosing spondylitis, idiopathic pulmonary arterial hypertension, and autoimmune disorders including multiple sclerosis exhibited enrichment, underscoring the significance of these genes in immune-mediated diseases. Moreover, certain non-inflammatory disorders such as diffuse large B-cell

lymphoma, diabetic retinopathy, and malignant neoplasm of the gastrointestinal tract had modest relationships, suggesting possible pleiotropic effects of the target genes[42].

Psoralen, a psoriasis-specific target, was linked to SOD1, which is crucial for the control of oxidative stress. Psoralen mitigates oxidative damage, a crucial element in the progression of psoriatic lesions, by interacting with superoxide dismutase. Diosgenin exhibited several targets, including MAPK8, TNF, and PTGS2. MAPK8, or JNK1, participates in stress-induced signaling and keratinocyte responses; TNF serves as a pivotal pro-inflammatory cytokine in the development of psoriasis; and PTGS2 (COX-2) facilitates prostaglandin production associated with inflammatory cascades. Collectively, these objectives highlight that Psoralen mostly regulates oxidative pathways, while Diosgenin affects inflammatory signaling, cytokine modulation, and immunological activation[43].

The combination of Psoralen and Diosgenin, analyzed by disease enrichment methods, significantly indicates their therapeutic potential for treating psoriasis. Psoralen functions via antioxidant pathways, whereas Diosgenin operates via anti-inflammatory and cytokine regulating systems. The complementarity of these processes endorses their synergistic therapeutic use in psoriasis and other immune-inflammatory disorders, underscoring their multi-target pharmacological potential[44].

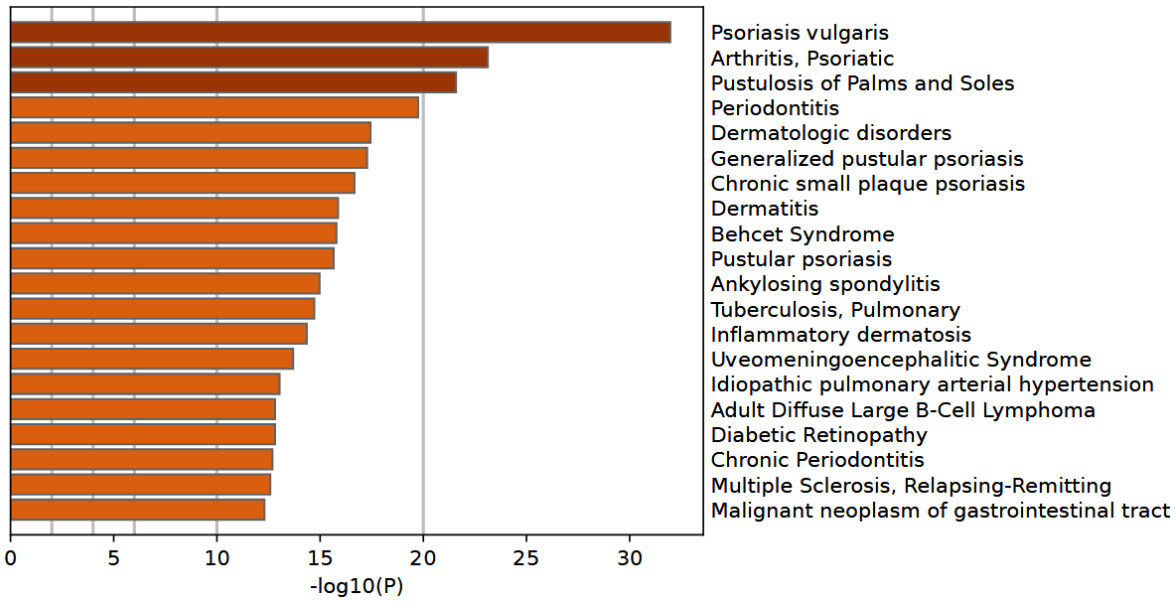

Figure 3: Gene ontology and disease enrichment analysis showing strong associations of Psoralen and Diosgenin targets with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and related immune-inflammatory disorders, highlighting their multi-target therapeutic potential in modulating oxidative stress and inflammatory pathways.

ADME analysis

The ADME (Absorption, Distribution, Metabolism, and Excretion) study of Psoralen and Diosgenin was conducted using the SwissADME computational tool, revealing their physicochemical and pharmacokinetic characteristics pertinent to drug-likeness and therapeutic efficacy.The radar map for Psoralen shows a balanced profile in terms of lipophilicity, molecular size, polarity, solubility, saturation, and flexibility [45]. The molecule exhibits intermediate lipophilicity and polarity, suggesting an optimal balance of membrane permeability and solubility. The comparatively small molecular size and reduced flexibility of psoralen indicate enhanced oral bioavailability, since stiff molecules often exhibit superior receptor binding and metabolic stability[46]. Moreover, Psoralen has considerable unsaturation, indicative of its aromatic composition, perhaps augmenting certain protein interactions. In the BOILED-Egg plot, Psoralen is situated in the yellow area (BBB), indicating its capacity to traverse the blood-brain barrier, while simultaneously being located inside the human intestinal absorption (HIA) zone. This dual property suggests that Psoralen could achieve good systemic exposure and CNS penetration[47].

Diosgenin exhibited a distinct ADME profile owing to its more substantial steroidal structure. The radar plot demonstrates increased lipophilicity relative to Psoralen, with a notable impact from size and mild polarity. Diosgenin has more insolubility than Psoralen, indicative of its hydrophobic steroidal structure, which may restrict water solubility while promoting partitioning into lipid membranes. Its flexibility and saturation are elevated, aligning with steroidal scaffolds that conform to receptor binding sites. In the BOILED-Egg plot, Diosgenin is located in the yellow BBB area, indicating permeability across the blood-brain barrier and

favorable intestine absorption (HIA). The pharmacokinetic prediction indicates significant lipophilicity, which enhances the potential for membrane transport and bioavailability[48].

Both metabolites were anticipated to be non-substrates of P-glycoprotein (PGP-), indicating a reduced likelihood of cellular efflux and hence facilitating optimal intracellular retention. The balanced WLOGP and TPSA values for both compounds further suggest oral drug-likeness. Psoralen, characterized by a smaller molecular weight and more polarity, may exhibit expedited systemic absorption, while Diosgenin, with a lipophilic steroidal structure, may facilitate prolonged interactions with lipid membranes and receptors[49].

The ADME research indicates that Psoralen and Diosgenin both satisfy advantageous drug-like parameters, exhibiting effective intestinal absorption, blood-brain barrier penetration, and absence of P-glycoprotein efflux. Psoralen is anticipated to have enhanced solubility and systemic distribution, while Diosgenin has more lipophilicity and receptor versatility. These pharmacokinetic features enhance their biological activity, underscoring their potential as treatment options for psoriasis and associated inflammatory illnesses[50].

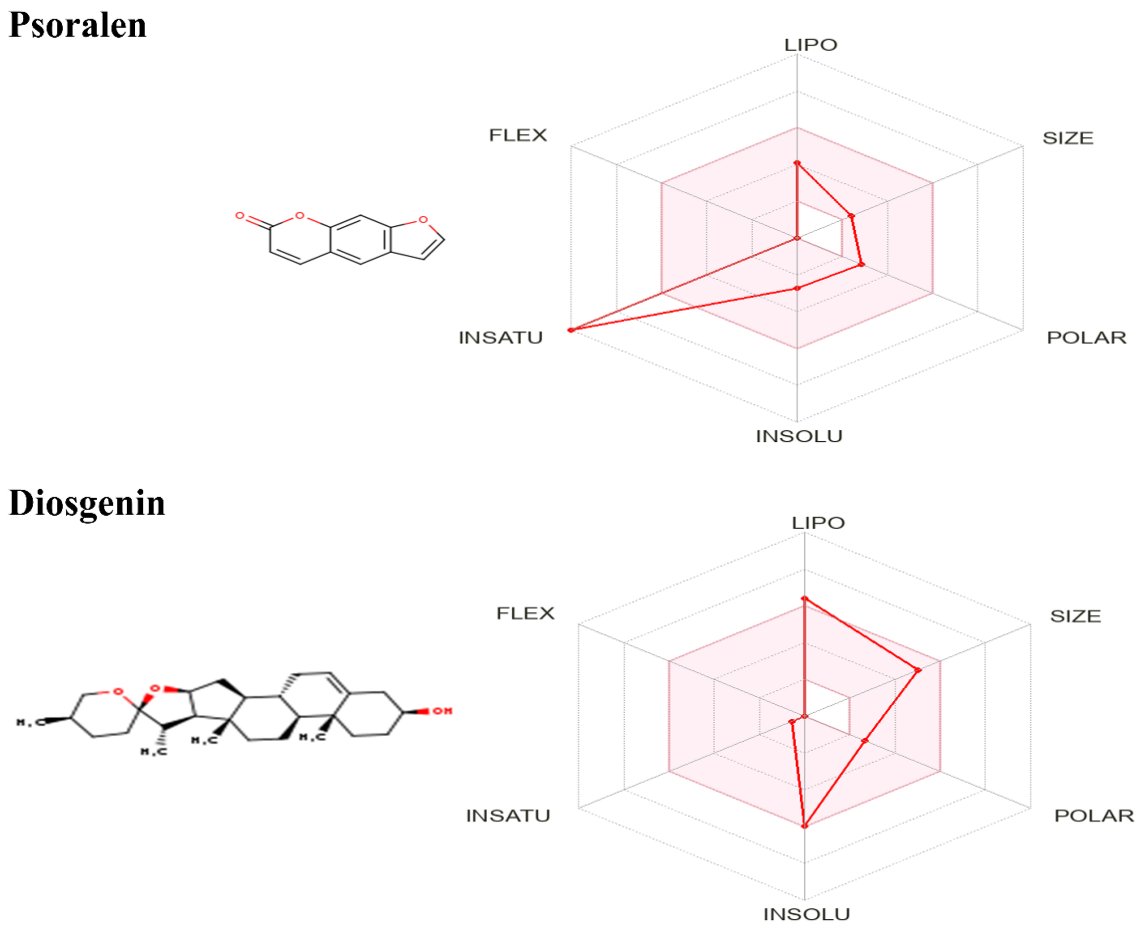

Figure 4: SwissADME radar plots showing physicochemical properties of Psoralen and Diosgenin, including lipophilicity, size, polarity, solubility, flexibility, and saturation, highlighting their favorable drug-like profiles and potential therapeutic suitability for psoriasis and inflammatory disorders.

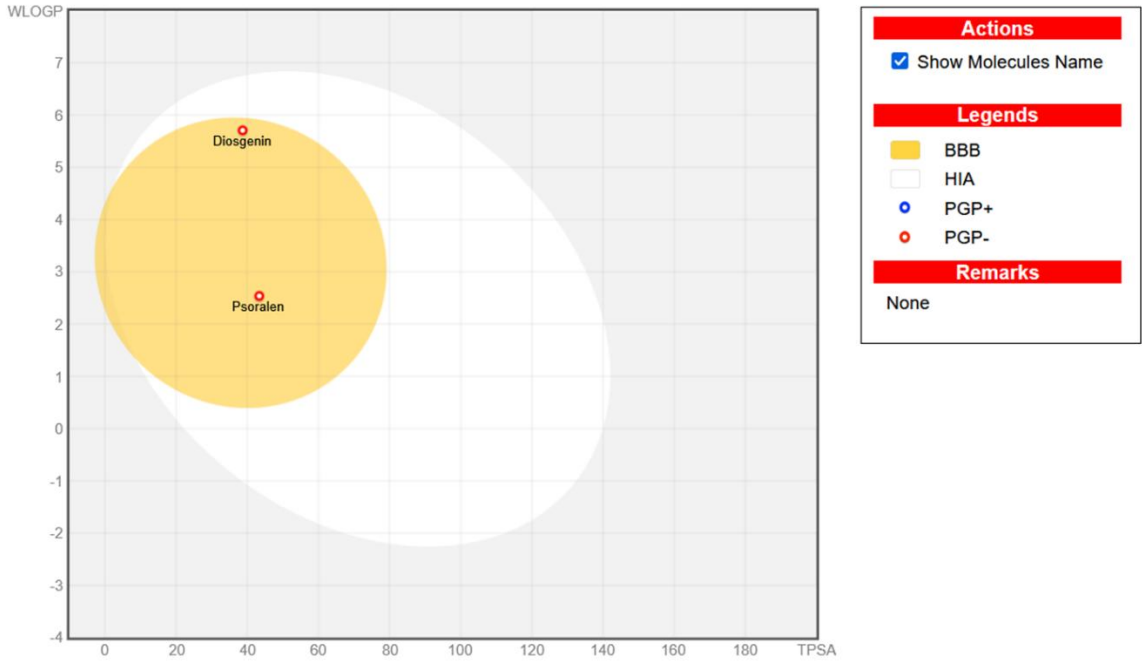

Figure 5: BOILED-Egg predictive model representing the pharmacokinetic profile of Diosgenin and Psoralen, where both molecules fall within the BBB-permeable zone, suggesting good gastrointestinal absorption and potential for blood–brain barrier penetration, enhancing their therapeutic relevance.

Table 2: ADME analysis of selected metabolites of Diosgenin and Psoralen

Molecule	Canonical SMILES	Formula	MW	TPSA	iLOGP	Consensus LogP	Bioavailability Score	GI absorption	BBB permeant
Psoralen	O=c1ccc2c(o1)cc1c(c2)cco1	C11H6O3	186.16	43.35	2.01	2.12	0.55	High	Yes
Diosgenin	C[C@@H]1CC[C@@]2(OC1)O[C@@H]1[C@H]([C@@H]2C)[C@@]2([C@@H](C1)[C@@H]1CC=C3[C@]([C@H]1CC2)(C)CC[C@@H](C3)O)C	C27H42O3	414.62	38.69	4.49	5.02	0.55	High	Yes

IV. Discussion

Psoriasis is a complex condition characterized by immunological dysregulation, keratinocyte hyperproliferation, and oxidative stress. The intricacy of its pathophysiology presents considerable obstacles in formulating viable therapies. Conventional therapy, including systemic immunosuppressants and biologics, focus on certain inflammatory pathways, such TNF-α, IL-17, or IL-23, however often face constraints due to adverse effects, elevated costs, and insufficient remission in specific patient demographics. The growing interest in natural products as multi-target therapeutic agents stems from their capacity to concurrently affect several biological processes, providing a safer and perhaps more effective alternative. This research used a network pharmacology approach to clarify the molecular processes via which Psoralen and Diosgenin have therapeutic benefits for psoriasis.

The protein–protein interaction (PPI) network analysis identified a densely linked system of psoriasis-related targets, with IL6, TNF, PTGS2, and STAT3 identified as important hub proteins. IL6 significantly enhances inflammatory signaling and stimulates keratinocyte growth, while TNF functions as a principal regulator of immunological responses, orchestrating the release of other pro-inflammatory cytokines. PTGS2 (COX-2) facilitates the production of prostaglandins, which enhance inflammation and discomfort, whereas STAT3 functions as a transcription factor that regulates cytokine-induced cellular responses. The discovery of these hub proteins corresponds with current research on the essential pathways implicated in psoriasis development and validates their potential as treatment targets.

The compound–target interaction research revealed that Psoralen mostly interacts with superoxide dismutase 1 (SOD1), an antioxidant enzyme that catalyzes the conversion of superoxide radicals into hydrogen peroxide and oxygen. Oxidative stress is a recognized factor in keratinocyte impairment and persistent inflammation in psoriasis. The direct interaction of Psoralen with SOD1 indicates that its therapeutic impact mostly arises from the modulation of oxidative stress, therefore inhibiting the formation of reactive oxygen species (ROS) that initiate inflammatory signaling pathways. This mechanism enhances its conventional use in dermatological conditions and offers a mechanistic foundation for its efficacy in mitigating oxidative damage in psoriatic lesions.

Diosgenin had a more extensive interaction profile, including MAPK8 (JNK1), TNF, and PTGS2. MAPK8 participates in cellular responses to stress and apoptosis, and its dysregulation leads to keratinocyte hyperproliferation and inflammatory signaling. The interaction between Diosgenin and TNF demonstrates its capacity to regulate a key pro-inflammatory cytokine in psoriasis. Diosgenin may diminish TNF expression or limit its function, so mitigating the inflammatory cytokine cascade and decreasing immune cell penetration into the skin. The interaction with PTGS2 indicates that Diosgenin may impede prostaglandin production, hence alleviating inflammation and discomfort linked to psoriatic plaques. The compound–target network demonstrated internal connection among TNF, MAPK8, and PTGS2, underscoring Diosgenin's involvement in influencing a complex subnetwork of inflammatory pathways rather than discrete targets.

Gene ontology and illness enrichment analyses further substantiated the significance of the selected targets in psoriasis and associated immune-inflammatory diseases. Psoriasis vulgaris had the greatest enrichment score, demonstrating the significant overlap of Psoralen and Diosgenin targets with molecular pathways associated with this illness. Other notably enriched disorders included psoriatic arthritis and pustulosis of the palms and soles, indicating that these chemicals may possess wider therapeutic potential in immune-mediated inflammatory diseases. The enhancement of pathways associated with cytokine-mediated signaling and keratinocyte proliferation underscores the chemicals' ability to affect both immunological and skin-resident cells, offering a dual strategy for disease control.

The ADME profiling data demonstrated advantageous pharmacokinetic characteristics for both drugs. Psoralen exhibited intermediate molecular weight and polarity, facilitating effective intestinal absorption and blood-brain barrier (BBB) penetration. Diosgenin, despite its increased lipophilicity and bigger molecular size attributed to its steroidal structure, demonstrated significant gastrointestinal absorption and blood-brain barrier penetration. Both compounds were anticipated to be non-substrates of P-glycoprotein, indicating they are unlikely to undergo cellular efflux processes that may restrict bioavailability. The pharmacokinetic characteristics are crucial for systemic disorders such as psoriasis, where medication absorption, distribution, and prolonged tissue concentration are essential for treatment efficacy.

The integrated findings from network pharmacology and ADME analysis highlight the multi-target, polypharmacological characteristics of Psoralen and Diosgenin. The antioxidant mechanism of psoralen enhances the anti-inflammatory actions of diosgenin, together offering a more comprehensive treatment approach to psoriasis etiology. The dual-targeting strategy concurrently treats the primary pathogenic factors of oxidative stress and chronic inflammation, which is essential because to the redundancy and compensatory characteristics of the signaling pathways implicated in psoriasis. The work offers persuasive in silico evidence of the chemicals' medicinal potential; nonetheless, experimental confirmation is crucial. In vitro experiments may evaluate the direct inhibitory effects of Psoralen and Diosgenin on SOD1 activity, TNF expression, and prostaglandin production. In vivo research using psoriatic animal models might elucidate their effectiveness, pharmacokinetics, and safety profile. Moreover, clinical studies will be essential to assess the actual efficacy of these drugs in psoriasis patients, specifically their capacity to diminish lesion severity, inflammation, and enhance quality of life.

This network pharmacology study identifies Psoralen and Diosgenin as viable multi-target options for psoriasis treatment. Their synergistic modes of action, advantageous pharmacokinetic characteristics, and participation in critical pathological pathways indicate their potential as useful therapeutic agents. This study advocates for more experimental research and clinical investigation, providing a systems-level framework for the advancement of safer, more complete therapies for intricate inflammatory conditions like psoriasis.

V. Conclusion

This research used a network pharmacology methodology to explore the multi-target therapeutic efficacy of Psoralen and Diosgenin in addressing psoriasis, a multifaceted immune-mediated inflammatory skin condition. Through the integration of protein–protein interaction (PPI) networks, compound–target interaction mapping, gene ontology (GO) analysis, disease enrichment, and ADME profiling, we offered a thorough systems-level comprehension of how these natural compounds may influence critical pathogenic mechanisms in psoriasis. Our findings indicated that Psoralen mostly targets superoxide dismutase 1 (SOD1), facilitating the alleviation of oxidative stress, a significant contributor to keratinocyte dysfunction and persistent inflammation

in psoriatic lesions. This antioxidant mechanism underpins Psoralen's potential as a preventative agent against ROS-induced tissue damage, consistent with its historical use in dermatological conditions. Diosgenin demonstrated a more extensive interaction network, including many significant targets including MAPK8, TNF, and PTGS2. These connections indicate Diosgenin's involvement in regulating inflammatory signaling pathways, cytokine generation, and prostaglandin synthesis, which are essential to the immunological dysregulation seen in psoriasis. The intrinsic connectedness of Diosgenin's targets suggests a synergistic impact, whereby concurrent regulation of interrelated pathways may enhance disease management. ADME analysis further validated that both compounds exhibit advantageous pharmacokinetic characteristics, including effective gastrointestinal absorption, permeability across the blood-brain barrier, and non-substrate status for P-glycoprotein, suggesting potential for substantial systemic bioavailability and therapeutic effectiveness.

The synergistic mechanisms of Psoralen and Diosgenin indicate that their combination use may provide a multi-targeted treatment approach for psoriasis. These results provide a compelling justification for more in vitro, in vivo, and clinical investigations to confirm their effectiveness and safety, facilitating the development of innovative, natural compound-based therapies for intricate inflammatory illnesses.

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Conflict of interest

The authors declare no conflict of interest.

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