Systems Level Analysis of Gene, Pathway and Phytochemical Associations with Psoriasis

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Abstract

Psoriasis is a chronic immune-mediated disorder characterized by systemic inflammation and keratinocyte hyperproliferation, yet the molecular basis of disease persistence and associated comorbidities remains incompletely understood. To identify regulatory axes beyond the classically targeted cytokines, we integrated transcriptomic profiling of lesional versus normal skin from the GSE14905 dataset with pathway enrichment, upstream regulator discovery, and network pharmacology using Qiagen's Ingenuity Pathway Analysis. Four differentially expressed genes *PRSS3P1*, *LINC0114*, *DANT2*, and *GK4P* were identified as having previously unreported gene-disease associations and two of them, *PRSS3P1* and *LINC01140*, mapped to inflammation and cell migration, suggesting pathogenic relevance. Pathway enrichment pointed to alternative inflammatory and immunometabolic circuitry beyond classical cytokine cascades, including C-type lectin receptor signaling, RIG-I-like receptor signaling and NOTCH3/RUNX3 transcriptional regulation. Upstream regulator analysis identified canonical cytokine drivers and additionally highlighted multiple previously unreported gene-disease regulators, including *IFNA10*, *IFNA14*, *IFNA16*,

IFNA21, *IFNA6*, *IFNA7*, *IFNL4*, *IFNL1* and *MRGPRA2A*. Network pharmacology combined with ADMET-AI screening prioritized seven multi-target phytochemicals (mahanine, taraxasterol, tricin, tamarixetin, annomontine, protopine, atractylon) with consistent direction-of-effect across key targets, while SynergyFinder analysis indicated preferential synergy for flavonoid-alkaloid combinations. Together, these findings identifies new disease-linked pathways and upstream regulators and proposes a systems-level framework for rational, multi-target, synergy-based phytochemical interventions for chronic psoriasis management.

Keywords: Psoriasis, Transcriptomics, Novel gene-disease associations, Interferon signaling, Upstream regulators, Immunometabolic pathways, Network pharmacology, Phytochemicals, Synergy analysis, Multi-target therapy

1 Introduction

Psoriasis is a long-lasting autoimmune disease that causes inflammation and affects more than just the skin. Approximately 2-3% of the global population is affected by psoriasis. It is more common among Caucasian people living at higher latitudes than it is among people living in Asia or Africa. [1, 2, 3, 4]. The disease is linked to several comorbidities, including cardiovascular diseases, metabolic syndrome, obesity, diabetes mellitus, inflammatory bowel disease, and non-alcoholic fatty liver disease [5, 6]. As a result, the quality of life for individuals with psoriasis is similar to that of other significant chronic conditions [7]. Epidemiological studies indicate two distinct peaks of disease onset: early adulthood (20-30 years) and later adulthood (50-60 years), suggesting that both genetic and environmental factors influence disease susceptibility and persistence [4]. Psoriasis develops from an ongoing interaction between genetic susceptibility and environmental factors, including infections, trauma, stress, and specific medications [8, 9]. Dendritic cells activate Th1 and Th17 lymphocytes and plasmacytoid cells that make type I interferon at the cellular level. These immune cells secrete cytokines, such as tumor necrosis factor-α (TNF-α), interleukins 17 and 23, interferon-γ, and other mediators, which collectively promote keratinocyte hyperproliferation and perpetuate chronic inflammation [10, 11]. The disease develops through a network of interconnected biological processes. Inflammatory molecules released from affected skin can enter the systemic circulation and influence distant organs. Crosstalk among immune cells, skin cells, and connective tissue cells sustains a pathogenic cycle that connects cutaneous inflammation with systemic conditions such as atherosclerosis and insulin resistance [2, 12]. Treatments for moderate-to-severe psoriasis have shifted from non-specific immunosuppressive agents to targeted biologic therapies that focus on individual cytokines. Biologic drugs targeting TNF-α, IL-17, or IL-23 superfamily members have demonstrated dramatic improvements in treatment response, leading to almost complete clearance in patients[13, 8]. However these drugs are not curative and result in recurrence following discontinuation [14]. Additionally, these drugs are associated with adverse reactions due to severe immune

suppression, cytotoxicity, or susceptibility to infections [14]. Current psoriasis treatments work well, but they mainly act on a small number of cytokines [9]. Research now shows that the disease involves much broader disruption, affecting not only interferon-related pathways but also metabolic regulators and pathways linked to cell growth [15]. This wider range of altered pathways suggests that treatments should be able to act on multiple biological processes at the same time. Phytochemicals, which are bioactive compounds derived from plants, offer this possibility because their complex structures allow them to act on several targets simultaneously. Traditional medical systems such as Ayurveda, Siddha, and Traditional Chinese Medicine have long used plant-based remedies to treat chronic skin conditions. For example, psoralen from *Psoralea corylifolia*, aloe emodin from *Aloe vera*, and curcumin from *Curcuma longa* are known for their anti-inflammatory and anti-proliferative effects [3, 16]. Other plant-based compounds like *Nigella sativa*, *Rubia cordifolia*, *Smilax china*, *Thespesia populnea*, and *Wrightia tinctoria* possess immune-modulatory properties for relieving patients with psoriasis [17, 18].Various plant-derived compounds, for instance, flavonoids, terpenoids, and alkaloids which have been shown to help modulate skin barrier homeostasis, alleviate oxidative stress, and properly control the activity of the immune system. These compounds demonstrated great prospective for treatment of inflammatory skin diseases such as psoriasis [19]. Many natural compounds, including flavonoids, coumarin derivatives, and polyphenolic compounds, have been reported to have significant effects on prominent inflammation-related signaling pathways involving NF-κB activation, cytokine production, and keratinocyte growth. They thus have been shown to properly restore skin architecture by maintaining cellular homeostasis [20]. However, less than 15% of these molecules are scientifically assessed for dermatological applications although plant-derived medicines represent nearly one-fourth of licensed drugs [19]. Contemporary breakthroughs in bioinformatics and network pharmacology allow for a rigorous mapping between phytoconstituents and genes related to diseases. For example, oleanolic acid, a triterpenoid compound, demonstrated efficacy in an imiquimod-induced psoriasis model and was shown to target MAPK3, STAT3, PPARG, and PTGS2 through network pharmacology and molecular docking [21]. Further, traditional plant extracts and individual compounds can be used as adjunt or maintenance therapies for chronic dermatoses with minimal adverse effects [22]. Phytochemicals, in terms of therapeutic delivery, have ideal attributes for skin-targeting therapies. They can be formulated for nanoparticle delivery, hydrogels, and lipid formulations with high local drug concentration but low systemic exposure, which is ideal for chronic skin disorders that require repeated use [20]. Plant-derived medications have attributes to modulate the immune system as well as other significant pathways implicated in oxidative stress pathways due to failed barriers, as required for chronic skin disorders such as chronic dermatitis [19]. Traditional polyherbal medicines such as *Parangichakkai Chooranam* are now conceptualized with omics approaches and systems biology to understand their immunomodulatory and metabolic functions [23]. Despite the advances, there are still uninvestigated regions in terms of using plant extracts in psoriasis treatment, especially in the isolation and identification of bioactive components [24, 25]. Modern computations have now integratively employed network pharmacology, three-dimensional pharmacophore modeling, and

systems-level pathway analyses together with molecular docking in understanding the mechanism action of phytochemicals in the treatment and management of inflammation in the skin[24, 26]. In psoriasis, for instance, scientists have now specifically targeted beyond general anti-inflammatory properties, and Wang et al. employed network analyses, where quercetin has depicted therapeutic efficacy through the concept of triple inhibition of signaling in Notch1, PI3K/Akt, and Glut-1[27]. Similarly, systems biology approaches have been applied to optimize multi-component therapies, as seen in the identification of a synergistic interaction between baicalin and echinacoside, which were predicted and experimentally validated to downregulate the IL-17 and TNF signaling pathways more effectively in combination than as monotherapies [28]. The utility of these *in silico* strategies extends to other skin conditions as well, validating the approach for complex inflammatory phenotypes. In acne vulgaris, network pharmacology combined with molecular dynamics simulations identified vaccenic acid as a potent inhibitor of bacterial virulence factors rather than a simple bactericide [29], while in vitiligo, integration of transcriptomics and docking revealed that flavonoids from purslane target the PI3K/Akt and PPAR signaling axes to protect melanocytes [30]. These studies collectively illustrate that bioinformatics-driven screening is a reliable method for identifying bioactive candidates, however, a comprehensive workflow that integrates differential gene expression with ADMET-based prioritization for topical delivery remains necessary to systematically shortlist the most promising candidates for translational development. Based on this logic, to widen the therapeutic scope of psoriasis, the approach adopted in this study combines transcriptomic analysis with network pharmacology. The objectives include the following: 1) validating known gene signatures for psoriasis and identifing novel differentially expressed genes and their corresponding regulatory genes. 2) explaining the pathways and interaction networks that underlie psoriasis biology. 3) associating psoriasis genes with phytochemicals, which are known to act on those genes and/or their corresponding pathways. 4) concentrating on multiple-targeting natural products, particularly phytochemicals designed for topical application. Evaluate the interaction among the selected phytochemicals in order to identify synergy and antagonism. By so doing, the approach identifies important phytochemicals in the plant and the rationale among them. These findings provide a solid starting point for future validation studies and the development of therapeutic strategies for psoriasis.

2 Results

2.1 Identification of outliers and sample clusters through PCA

Principal Component Analysis (PCA) highlights a clear separation between psoriasis and control groups Figure 1A. Lesional samples (red) were segregated from normal samples (green) and uninvolved samples (blue), representing transcriptomic changes mediated by biological pathways due to disease. Uninvolved skin samples largely overlapped with the healthy group, suggesting minimal transcriptomic alteration in these regions. Three lesional samples deviated from the main lesional cluster and were identified as outliers. These outlier samples were excluded from further analyses to minimize variability in downstream analyses (Refer to Section 3.1).

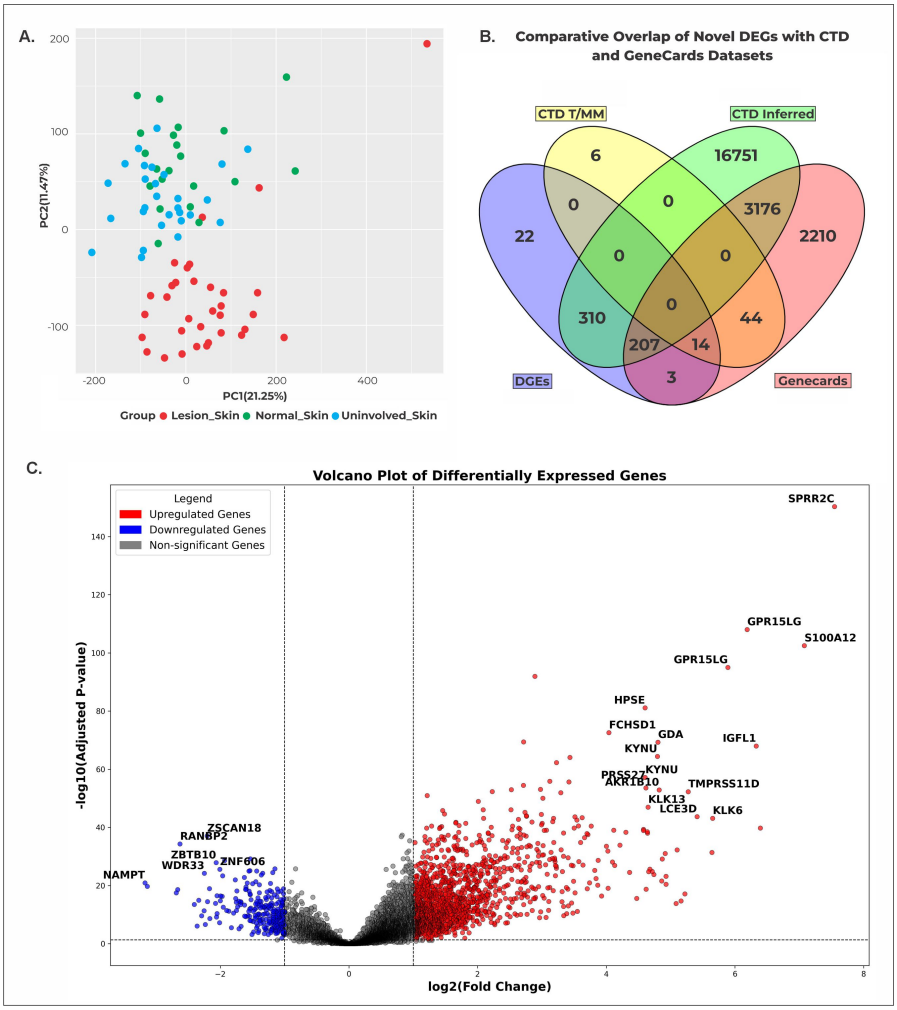

Fig. 1 Transcriptomic profiling and identification of genes showing new gene-disease associations in psoriasis. Overview of transcriptomic analysis and gene set comparison in psoriasis. (A) PCA illustrating separation of lesional, uninvolved, and normal skin samples. **(B)** The Venn diagram shows the overlap between DEGs identified in this study and genes previously linked to psoriasis in the CTD and GeneCards databases. **(C)** The volcano plot shows differences in gene expression between lesional skin and normal skin samples.

2.2 Identification of Gene Targets of Psoriasis through DGE Analysis and IPA

Differential gene expression (DGE) analysis was used to compare lesional skin with normal skin. In total, 556 genes showed significant changes in expression, including 270 upregulated genes and 286 downregulated genes. The complete list of DEGs, along with their $\log_2$ fold-changes and adjusted p-values, can be found in Sheet 1 of Supplementary File 1. (Refer to Section 3.2). The volcano plot (Figure 1C) indicates

the location of the DEGs and those genes with significant expression variation, as determined by statistical analysis, are shown. The genes with adjusted p-value < 0.05 and $\log_2$ fold-change > 2 were regarded as significant, with red color representing upregulated and blue representing downregulated genes. To better understand the role of these DEGs, we overlaid the 556 genes with those involved in psoriasis, obtained from not one but two authoritative gene databases, the Comparative Toxicogenomics Database (CTD) and GeneCards [31] [32]. CTD contained 20,555 psoriasis-associated genes, of which 63 had direct evidence as markers or mechanisms, one had therapeutic evidence, and 20,491 were classified as inferred associations. GeneCards listed 5,654 psoriasis-related genes.

A comparative overlap analysis was performed using Venny to identify shared and unique gene sets [33]. As the primary goal was to identify phytochemicals with new disease-associations and potential therapeutic relevance, the focus was on two key intersections: (a) DEGs-exclusive genes, representing genes showing new gene-disease associations that do not appear in CTD (inferred) or GeneCards (22 genes), and (b) DEGs intersecting CTD marker/mechanism/therapeutic (M/M/T) evidence, representing high-confidence psoriasis genes (14 genes overlapping DEGs, CTD MM/T, and GeneCards).

To refine the biological relevance of the 22 DEGs-exclusive candidates, PubMed-based literature screening was performed. This revealed that only four of these genes *DANT2, GK4P, PRSS3P1, and LINC01140* had no previous PubMed-indexed linkage to psoriasis. These transcripts showed marked differential expression (DANT2: $\log_2$FC = -2.562, p = 3.02E-23; GK4P: $\log_2$FC = 2.618, p = 1.20E-19; PRSS3P1: $\log_2$FC = 2.224, p = 1.85E-40; LINC01140: $\log_2$FC = -2.289, p = 3.76E-10). All identified intersection points are shown in the Venn diagram above (Figure 1B), and the complete list of DEGs, along with the subset of genes showing new gene-disease associations, is provided in Sheet 2 of Supplementary File 1. Beyond those sets, further literature mining was undertaken, and those genes with new associations within the overlapped categories that had not been reported in previous literature regarding psoriasis were identified. As shown in the Venn Diagram, (Figure 1B), amongst the 310 common genes between DEGs and CTD inferred genes, 179 genes reported new gene-disease associations without any citations in psoriasis literature. Similarly, among 207 common elements shared by DEGs, CTD inferred, and GeneCards, 29 pathways showed no prior PubMed evidence linking them to the disease, indicating potentially new pathway-disease associations. The 179 and 29 genes showing new gene-disease associations, together with the 14 high-evidence genes (shared across DEGs, CTD M/M/T, and GeneCards), were selected for further analysis. This combined gene set was then used to identify known phytochemicals acting on genes showing new gene-disease associations, as well as phytochemicals newly linked to known psoriasis genes. To obtain a systems-level view of the lesional psoriatic transcriptome, we performed KEGG and Reactome pathway enrichment on the full set of 556 DEGs between lesional and normal skin. As expected, KEGG analysis recovered canonical inflammatory modules of psoriasis. IL-17 signaling, Toll-like receptor signa, NOD-like receptor signaling, and TNF signaling were significantly enriched, corresponding to Th17/IL-17-driven keratinocyte inflammation, innate immune activation, inflammasome-linked signaling,

and TNF-centered cytokine networks. Additional KEGG pathways, including osteoclast differentiation and apoptosis, are consistent with psoriatic arthritis-associated bone remodeling and altered keratinocyte survival. Beyond these canonical axes, the 556-gene set also enriched antiviral and pattern-recognition pathways, including the C-type lectin receptor signaling pathway (*PYCARD, JUN, CLEC7A*) and the RIG-I-like receptor signaling pathway (CXCL10, NLRX1). Systematic PubMed screening indicated that these pathways have not been explicitly reported in psoriasis, supporting their annotation as candidate novel pathway-disease associations. Reactome analysis similarly highlighted interferon alpha/beta signaling and NOTCH3-related transcriptional modules. Notably, the NOTCH3/RUNX3 signaling axis has not previously been described in the context of psoriasis and was therefore classified as a candidate novel Reactome association. To refine the enrichment signal and reduce dataset-specific noise, KEGG analysis was then repeated on the 179-gene subset representing DEGs with new gene-disease associations. This refined signature revealed enrichment of pathways converging on metabolic, endocrine, and neuro-immune regulation. Among these, ovarian steroidogenesis emerged as a candidate novel pathway-disease association (*HSD17B1, INSR*), suggesting previously unrecognized links between sex-steroid metabolism and psoriatic inflammation. Additional enriched pathways included insulin resistance, insulin signaling, arginine and proline metabolism, pyrimidine metabolism, carbohydrate digestion and absorption, mineral absorption, and multiple neurotransmission-related pathways (dopaminergic synapse, nicotine addiction, cocaine addiction, long-term potentiation, and retrograde endocannabinoid signaling), indicating potential interactions between metabolic regulation, neuronal signaling, and cutaneous immune responses. To derive a compact and robust disease signature, we intersected the 29 and 14 gene subsets and focused on their overlap, yielding a 43-gene "core" module consistently dysregulated across independent comparisons. KEGG enrichment of this core module dominated by inflammatory inflammatory signaling pathways, including IL-17, TNF, NOD-like receptor, Toll-like receptor, and NF-κB signaling, delineating a tightly coupled cytokine network characteristic of chronic inflammatory disease. In parallel, enrichment of HIF-1 signaling, FoxO signaling, peroxisome, and longevity-regulating pathways linked this core module to hypoxia responses, oxidative stress, and metabolic regulation. Of particular interest, the "AGE-RAGE signaling pathway in diabetic complications" (*IL6, CXCL8, VEGFA*) emerged as a candidate novel pathway-disease association with no prior PubMed or CTD evidence directly linking this pathway to psoriasis. This finding suggests that advanced glycation end products and RAGE-mediated endothelial activation may provide a mechanistic bridge between cutaneous inflammation, oxidative stress, and cardiometabolic comorbidities frequently observed in psoriatic patients. Additional metabolic pathways, including non-alcoholic fatty liver disease and the longevity-regulating pathway, further support an interface between local tissue inflammation and systemic metabolic remodeling. A consolidated KEGG/Reactome enrichment table summarizing all three analyses (556 DEGs, 179-gene subset, and 43-gene core module), with pathway statistics, contributing genes, and novelty status, is provided in Supplementary File 2

2.3 Identification of regulatory networks and upstream drivers through IPA

To extend the DEG-based findings, the complete list of DEGs (with $\log_2$ fold-change and p-values) was analyzed using IPA. The platform generated results across the Graphical Summary, Upstream Regulators, Canonical Pathways, Diseases & Biofunctions, and ML Disease Pathways panels. (Refer to Section 3.5).

Overview of major regulatory programs - IPA Graphical Summary

The IPA Graphical Summary (Figure 2) revealed a coordinated activation of the type I/III interferon axis and associated antiviral programs in psoriatic lesions. Predicted activated nodes (orange) were centered on *STAT1*, *IRF1*, *IRF3*, and *IRF7*, indicating robust transcriptional activation of interferon-stimulated genes. Upstream viral-sensing components, including *cGAS/CGAS* and *MAVS*, converged on these central regulators, suggesting canonical activation of the cytosolic DNA and RNA sensing pathways. Multiple interferon ligands (*IFNA* subtypes and *IFNL1*) connected to downstream biological functions annotated as Interferon alpha/beta signaling, Antiviral response, and Antimicrobial response, consistent with an interferon-driven inflammatory milieu. A single node, *F3* (tissue factor), was predicted inhibited (blue), while most edges represented inferred or indirect regulatory relationships consistent with the directionality of our differential expression results. Collectively, the network supports a strong interferon-mediated transcriptional signature and provides a mechanistic scaffold linking the identified upstream regulators to downstream DEGs in psoriasis.

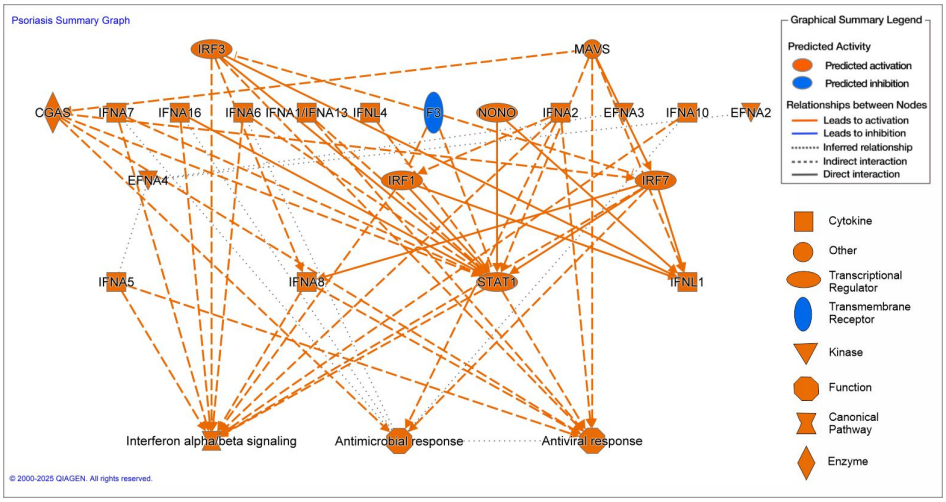

Fig. 2 Graphical summary generated by IPA showing predicted upstream regulators and functional interactions in psoriasis.

IPA Upstream Regulators: Evidence Mapping and Novel Associations

IPA identified a total of 230 upstream regulators (URs). To contextualize their psoriasis relevance, all URs were cross-compared against major knowledge bases (CTD M/M/T, CTD inferred and GeneCards). The full mapping of URs across tiers is provided in Supplementary File 3. PubMed screening of the IPA-exclusive tier identified 8 upstream regulators with no prior psoriasis linkage: *IFNA10*, *IFNA14*, *IFNA16*, *IFNA21*, *IFNA6*, *IFNA7*, *IFNL4*, *MRGPRA2A* and *IFNL1*. These were therefore designated as *upstream regulators with new disease associations* in the context of psoriasis. Despite the absence of prior PubMed-indexed evidence, several of the eight novel regulators showed strong causal prominence within IPA network layers. Interferon-alpha family members (*IFNA10*, *IFNA14*, *IFNA16*, *IFNA21*, *IFNA6*, *IFNA7*) and *IFNL4* projected onto antiviral and epithelial-immune crosstalk modules, whereas *MRGPRA2A* mapped to mast-cell-linked inflammatory signaling. Their convergence onto immune, epithelial, and inflammatory nodes indicates potential mechanistic relevance and positions these regulators as previously unrecognized upstream drivers of psoriatic inflammation.

Association of IPA regulators with potential phytochemical targets

The UR catalog (known vs. upstream regulators with new disease associations) were used analogously to the DEG framework to prioritize phytochemicals: (i) Map known phytochemicals to upstream regulators showing new disease associations, and (ii) Propose phytochemicals with new disease associations for known or high-evidence URs, with emphasis on inferred relationships and direction-of-effect consistency.

2.4 Prioritization of phytochemicals through CTD-based mapping

To identify potential phytochemical candidates targeting psoriasis-associated genes, a systematic chemical-gene mapping was performed using the CTD. First of all, the genes showing new gene-disease associations (from both DEGs and URs) were queried in CTD through a batch search. This analysis retrieved 1,569 chemicals predicted to interact with these genes. Next, these 1,569 chemicals were compared against 6,284 psoriasis-associated chemicals already reported in CTD. Among these, 6,200 had inferred evidence (interactions derived through curated gene links), while 17 were classified as marker/mechanism and 75 as therapeutic chemicals according to CTD's definitions. From this comparison, 1,296 overlapping chemicals were identified-meaning these chemicals interacted with genes showing new disease associations but were already known in CTD for psoriasis. After filtering these through Dr. Duke's Phytochemical Database for relevant biological activities (anti-inflammatory, antioxidant, antiproliferative, antimicrobial, anti-angiogenic, and antipruritic), 84 phytochemicals remained. NOTE: It is important to note that these 84 phytochemicals were already listed in CTD for psoriasis but only through inferred associations, not as marker/mechanism or therapeutic chemicals. Across these 84 phytochemicals, antioxidant and anti-inflammatory activities dominated, frequently co-occurring with antiproliferative and anti-angiogenic effects. Representative multifunctional agents included

curcumin, *quercetin*, *genistein*, and *resveratrol*. Details of these phytochemicals and their combined biological activities are provided in Supplementary File 4). Next, we investigated phytochemicals that target genes with new disease associations and were not previously reported in CTD or psoriasis literature. However, no such new phytochemicals were identified in this category. The workflow was then repeated for the known psoriasis-associated genes (known DEGs and known URs) to identify phytochemicals that have not yet been documented in CTD or psoriasis literature as targeting these genes. In this case, CTD returned 1,821 chemicals, which were filtered through Dr. Duke's catalogue to yield 27 phytochemicals with relevant biological activities. After literature verification, 13 of these phytochemicals were confirmed as newly linked to psoriasis, meaning they had not been previously reported in association with this disease. These 13 newly linked phytochemicals were: annomontine, olivetol, protopine, hypaconitine, taraxasterol, atractylon, carboxyatractyloside, mahanine, bilobalide, robinetin, scutellarein, tamarixetin, and tricin. Finally, these compounds were prioritized for further study based on (i) consistency with the direction of gene regulation (e.g., inhibitors for activated upstream regulators or upregulated DEGs), (ii) pathway relevance, and (iii) drug-like or topical suitability properties. (Refer to Section 3.6)

Selection of lead compounds based on direction-of-effect consistency

To further characterize the relevance of the 13 phytochemicals with new disease associations, their interaction patterns with psoriasis-associated DEGs and URs were examined. The directionality of the effect on gene expression (upregulation and downregulation) was assessed relative to the reported molecular actions of each phytochemical and compared against the directionality of the reported effect. Phytochemicals that counteracted the disease-associated expression profiles, either suppressing the overexpressed genes and promoting the underexpressed genes, were prioritized, and those that further exacerbated the disorder could be deprioritized. Based on the performed screening, the seven phytochemicals with newly discovered disease connections were prioritized, namely mahanine, taraxasterol, tricin, tamarixetin, annomontine, protopine, and atractylon. The shortlisted compounds demonstrated directionally consistent effects on key psoriasis-associated targets: (i) downregulation of overexpressed proliferative genes (*CCNB1*, *CDK1*); (ii) inhibition of matrix-remodeling and inflammatory mediators (*MMP9*, *PTGS2*); and (iii) upregulation or restoration of detoxification and signaling genes (*CYP1A1*, *CREB1*). Collectively, these phytochemicals exhibit complementary mechanisms aligned with psoriasis pathobiology, namely anti-proliferative, anti-inflammatory, and antioxidant effects, making them promising candidates for further validation in the context of topical or systemic therapy. Furthermore, *CREB1* was identified as an upstream transcriptional regulator targeting several DEGs, including *ADM, APOLD1, ARG1, ATF3, AURKA, BHLHE40, BIRC5, CCN1, CCNA2, CCNB1, CCNB2, CD3D, CHRM3, CXCL8, DUSP1, EGR1, ESRRG, FASN, FLT1, FOS, FOSB, GADD45B, GAL, GDA, GLDC, HSD11B1, IL6, INA, JUN, LCN2, LPL, MKI67, MMP1, NFIL3, NR4A1, NR4A2, PCK1, PER1, PPARG, PPARGC1A, PPP1R15A, PTGS2, RBP4, SIK1, SLC2A3, SMPD3, SOCS2, SOD2, STC1, TF, VEGFA, ZFP36*, among others, which are also targeted

by the phytochemicals with new disease associations identified through DEG analysis. The complete gene targets, their corresponding fold changes, and the molecular effects exerted by the phytochemicals are summarized in Table 1.

Table 1 Shortlisted phytochemicals, their target genes, fold-change values, and reported molecular effects. These compounds were prioritized based on direction-of-effect consistency and pathway relevance.

Phytochemical	**Target Gene**	**Fold Change ($\log_2$)**	**Reported Molecular Effect / Interaction**
Mahanine	CCNB1	+3.005	Decreases expression of CCNB1 protein (reverses upregulation).
Mahanine	CDK1	+2.343	Decreases expression and phosphorylation of CDK1 protein (reverses upregulation).
Taraxasterol	MMP9	+2.043	Inhibits TGFB1-mediated upregulation of MMP9 (reverses overexpression).
Tricin	PTGS2	−2.420	Inhibits PTGS2 transcription induced by TPA (normalizes inflammatory signaling).
Tamarixetin	PTGS2	−2.420	Decreases PTGS2 enzymatic activity (anti-inflammatory effect).
Annomontine	CYP1A1	−4.622	Increases expression of CYP1A1 mRNA (restores detoxification potential).
Protopine	CYP1A1	−4.622	Increases expression of CYP1A1 mRNA (restores detoxification potential).
Atractylon	CREB1	−3.293	Increases expression of CREB1 modified protein (restores signaling balance).

Evaluation of shortlisted phytochemicals for topical suitability using ADMET-AI

To evaluate the suitability of the shortlisted phytochemicals with new disease associations for topical application, physicochemical and pharmacokinetic properties were analyzed using the *ADMET-AI* platform. Key parameters-including molecular weight,

LogP, topological polar surface area (TPSA), hydrogen bond donors and acceptors, predicted skin permeability, and toxicity endpoints were assessed. The complete ADMET profiles of all compounds are provided in *Supplementary File 5*.

Screening revealed that protopine and atractylon exhibited the most favorable physicochemical profiles for passive dermal penetration, with optimal LogP, low TPSA, minimal toxicity alerts, and balanced lipophilicity, positioning them as strong candidates for topical formulation. Mahanine satisfied various physicochemical criteria, but its lipophilicity was at the borderline level with respect to LogP values above 6, which implies that either aqueous penetration enhancers or nano-formulations could be required to ensure its good penetration into the skin. Annomontine was shown to be safe and permeable, with moderately high AMES values and lower anti-inflammatory potency, making it more suited towards secondary functions. By contrast, tricin and tamarixetin, with high relevance to biological pathways in psoriasis, possessed high values of TPSA (> 100 Å^2), making them poor at penetrating intact skin by passive diffusion. Taraxasterol, although active, possessed very high lipophilicity with $\log P = 8$, making it difficult to absorb through intact skin without active technology. Therefore, these compounds are not suitable as standalone topical actives but may still contribute mechanistic insights or be incorporated through specialized delivery systems. The results from the ADMET studies aided in the prioritization of the phytochemicals in terms of those with optimal dermal applicability. (Refer to Section 3.7)

2.5 SynergyFinder (ZIP Model) Identifies Selected Phytochemical Combinations with Synergy

In order to explore the possible synergy among the bioactive compounds, an in silico synergy screen was performed using the Synergy Finder tool, in the ZIP model, on the final collection of seven phyto-compounds, namely, mahanine, taraxasterol, tricin, tamarixetin, annomontine, atractylon, and protopine. While some phytocompounds like tricin, tamarixetin, and taraxasterol are less useful alone in the topical formulation under the ADMET conditions, they were still included in the synergy screen because they strongly confer with the role they play in the psoriasis pathway and could provide an additive effect in combination with other phytocompounds that could better penetrate the skin. The analysis produced two types of synergy outputs: (i) concentration-dependent synergy score matrices that depicted variations in the ZIP synergy scores for various concentration pairs, and (ii) summary synergy scores that depicted mean and 'most synergistic area' synergy scores for each pair of phytochemicals. In the concentration-dependent synergy score matrix, filtering was applied to select only those pairs that had absolute ZIP scores > 5, signifying high synergy (positive ZIP) or antagonism (negative ZIP) interactions. From the results of the filtered pairs, the highest levels of synergy were shown by the tamarixetin-annomontine combination, with ZIP scores > 10.67 when 300nM tamarixetin and 1nM annomontine were used, and continued synergy throughout the range of 3-30nM annomontine, with ZIP scores of 8.09 to 7.86. This was in association with very high levels of percent inhibition (approximately 66-69%).The mahanine-tamarixetin combination also demonstrated strong synergistic behaviour, particularly at 3 nM mahanine with

300 nM tamarixetin, where the ZIP score reached 7.78. This further supports a measurable enhancement effect at sub-saturating concentrations of the potent compound mahanine. Among the other potent copairs, the tricin-protopine combination showed synergy scores of 7.51 (300/1 nM) and 6.23 (300/10 nM), accompanied by relative inhibition values exceeding 70%. The taraxasterol-tamarixetin pair also demonstrated extensive synergy, with a ZIP value of 7.10 at the 300/300 nM dose, along with additional scores > 5 across multiple dose ratios. Furthermore, the tricin-annomontine combination (ZIP = 6.51 at 300/300 nM; 5.73 at 100/1 nM) and the tricin-tamarixetin pair (ZIP = 6.50 at 300/100 nM) reinforced the consistent synergistic contribution of tricin when paired with either flavonoid or alkaloid partners. Moderate to high, yet consistently stable, synergy scores (ZIP $= 5-6$) were also observed for the copairs mahanine-protopine and mahanine-tricin, Notably, synergistic effects were predominantly asymmetric, typically involving higher concentrations of polyphenolic compounds (e.g., tricin or tamarixetin) paired with lower doses of alkaloids (e.g., annomontine or protopine), suggesting complementary mechanisms of action between antioxidant and bioactive scaffold chemotypes. Conversely, strong negative ZIP scores (≤ -5) were observed primarily for atractylon-associated pairs, including tricin-atractylon and mahanine-atractylon, with values as low as -8.72, implying possible antagonistic or competitive interactions. Additional antagonistic interactions were identified for protopine-atractylon, taraxasterol-tricin, and mahanine-annomontine pairs, particularly at high or equimolar concentrations ($\geq$100 nM). These results prove the dose-dependent and dose-ratio-dependent antagonism, and optimization on dose ratios is important to maintain cooperative action on the pharmacodynamics. The detailed synergy matrix on concentration levels, including the relative inhibition, synergy, and units, has been provided in **Supplementary File 6**.

SynergyFinder Summary: Top-Ranked Pairs Highlight Flavonoid-Alkaloid Complementarity

To identify overall trends across the matrix experiments, mean ZIP synergy scores for each phytochemical pair were computed and visualized as a ranked bar plot (Figure 3). The summary analysis revealed the top three pairs with the highest mean ZIP values, and they were protopine-annomontine (1.388), annomontine-tamarixetin (1.262), and tricin-mahanine (1.201). The next closest pairs were protopine-tricin and protopine-mahanine (0.792), and all pairs showed high synergy at different points.

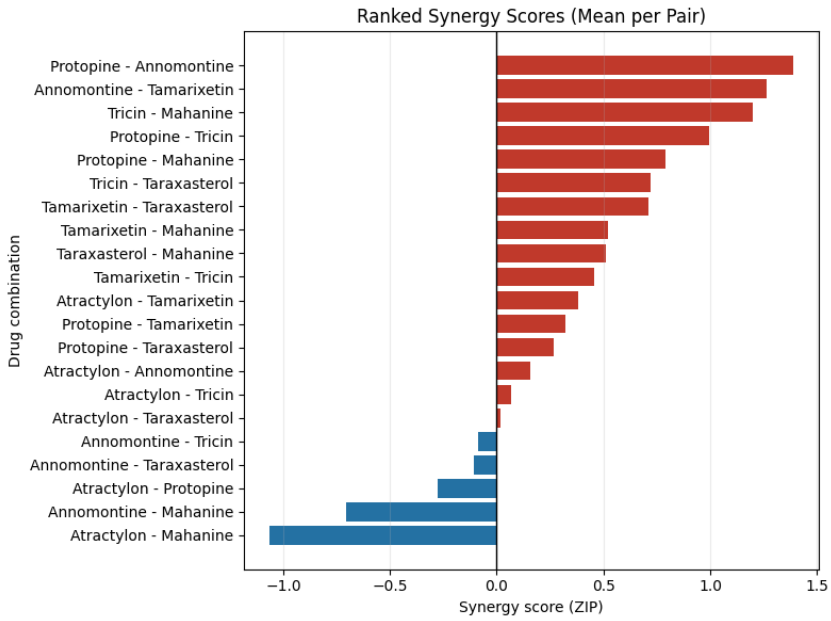

Fig. 3 Ranked ZIP synergy scores among phytochemical pairs.

The moderately synergistic pairs include tricin-taraxasterol, tamarixetin-taraxasterol, tamarixetin-mahanine, and taraxasterol-mahanine, whose synergy scores range from 0.45 and 0.72. On the other hand, pairs like atractylon-mahanine (-1.062), annomontine-mahanine (-0.706), and atractylon-protopine (-0.275) appeared to have overall antagonistic effects. From the presented findings, it appears that the careful combination of phytochemicals, especially those using the structures of the said classes, could potentially act in synergy in therapeutic ways. The combinatory pairs with high synergy scores could potentially prove useful in in vitro and in vivo studies aiming to determine their mechanisms and application in combinatorial therapeutic formulations.(Refer to Section 3.8)

2.6 IPA-Pathway Signals Cross-Mapped to Phytochemicals and Targets

Integration Across IPA Canonical Pathways, Diseases & Biofunctions, and ML Pathways

To contextualize the psoriasis DEGs, IPA outputs were examined across three knowledge layers: Canonical Pathways (CP), Diseases & Biofunctions (DB), and Machine Learning Pathways (ML). The analysis cross-mapped these pathway signals with genes targeted by the shortlisted phytochemicals with new disease associations to identify both direct and indirect modulation of DEG modules. To further link these pathways to potential intervention points, a list of phytochemical gene targets was compiled from both DEGs (*CCNB1*, *CDK1*, *MMP9*, *PTGS2*, and *CYP1A1*) and the

upstream regulator *CREB1* identified by IPA. Inclusion of *CREB1* expanded the target space to encompass downstream transcriptional networks indirectly influenced by phytochemicals.

Canonical Modules (IPA): IL-17, Interferon, Antimicrobial Defense, Keratinization

Canonical Pathway (CP) enrichment was dominated by immune-barrier and antiviral modules that are well established in psoriasis, including Antimicrobial Peptides, Interferon α/β Signaling, Interferon γ Signaling, Keratinization, and Role of IL-17A in Psoriasis. Sentinel DEGs mapping to these axes included *LCN2* (Antimicrobial Peptides), *EGR1* (Interferon α/β signaling), and *CXCL8* (IL-17A axis), consistent with heightened innate defense mechanisms and sustained type I/II interferon tone in lesional skin. In contrast, the OAS Antiviral Response pathway emerged as enriched despite the absence of prior curated literature explicitly linking this module to psoriasis, suggesting a potentially underappreciated contribution of oligoadenylate synthetase-mediated antiviral signaling in the psoriatic transcriptome. Many genes within these enriched pathways are either direct phytochemical targets or indirectly modulated via the upstream regulator *CREB1*, which controls a subset of these DEGs. The pathway-level overview is shown in Figure 4A, and the complete list of enriched canonical pathways is provided in **Supplementary File 7**

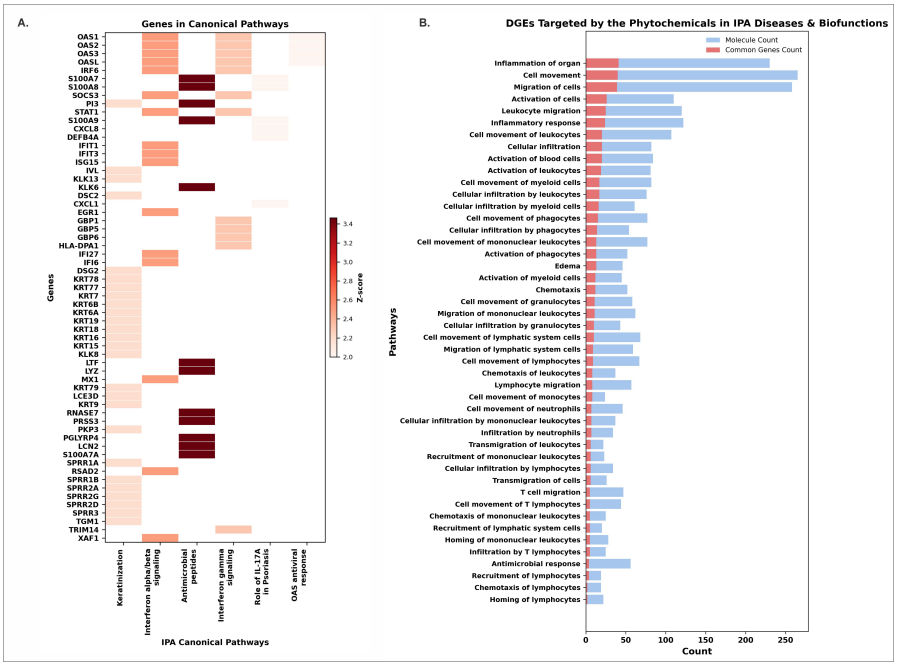

Fig. 4 Integration of canonical pathway and disease-biofunction enrichment results from IPA. (A) Heatmap showing psoriasis-associated DEGs mapped to significantly enriched IPA Canonical Pathways. Color intensity represents activation z-scores, where darker shades indicate higher predicted activation. **(B)** Bar plot illustrating IPA Diseases & Biofunctions terms associated with DEGs targeted by the shortlisted phytochemicals. Bars represent molecule counts (blue) and common overlapping gene counts (red), highlighting enrichment in inflammation, immune cell activation, and cellular infiltration processes characteristic of psoriasis.

Diseases & Biofunctions (IPA): Inflammation, Leukocyte Trafficking, Tissue Remodeling

The DB enrichments validated characteristic inflammation in psoriasis, with activation scores positively predicting participation in Inflammation of Organ, Inflammatory Response, and leukocyte behaviors such as Leukocyte Migration, Cell movement/migration, Cellular Infiltration, Chemotaxis, and Transmigration. Two DEGs having new disease associations *PRSS3P1* and *LINC01140* were also enriched in DB outputs. *PRSS3P1* appeared under **Inflammation of Organ**, whereas *LINC01140* featured under **Cell Movement**, **Migration of Cells**, and **Inflammatory Response**, indicating previously unreported participation of these transcripts in inflammatory and migratory programs relevant to psoriasis. Notably, a substantial subset of enriched DB categories—particularly those related to leukocyte activation, migration, homing, recruitment, cellular infiltration, and transmigration across multiple immune cell types (including lymphocytes, T lymphocytes, granulocytes, neutrophils, phagocytes, and mononuclear leukocytes) lacked prior curated literature explicitly linking these biofunctions to psoriasis. This suggests that while immune-cell trafficking is a well-recognized feature of psoriatic pathology, the fine-grained cellular movement

and infiltration programs captured here may represent under-annotated or previously unresolved dimensions of disease biology revealed by transcriptome-wide analysis. The DB results are summarized in Figure 4B and detailed in **Supplementary File 8**. The ML pathway layer further converged on immunometabolic and comorbidity associated themes commonly associated with psoriasis, including Oxidative Stress, Neuroinflammation, Allergic Inflammation, and metabolic traits such as Insulin Resistance, Hypertriglyceridemia/Hyperglyceridemia, Metabolic Syndrome X, Familial Insulin Resistance, and Hyperglycemia. Overlapping DEGs that were also phytochemical targets included *PPARG*, *PPARGC1A*, *SOD2*, *IL6*, *PTGS2*, *CXCL8*, *VEGFA*, *LPL*, *FASN*, and *PCK1*, underscoring the inflammation-metabolism interface central to psoriatic pathology. The complete list of ML-derived disease and pathway annotations, including both established and previously unreported associations, is provided in **Supplementary File 9**.

Integrated View (IPA+CTD): Chemokine-Cytokine-Matrix Circuitry and Immunometabolic Stress

Intersecting phytochemical targets with CP, DB, and ML results revealed concentrated convergence on: (i) Inflammatory trafficking and activation (DB: Inflammation of Organ, Inflammatory Response, Leukocyte Migration, Cellular Infiltration), (ii) Oxidative-stress/Immunometabolic ML pathways (Oxidative Stress, Insulin Resistance, Hypertriglyceridemia/Hyperglyceridemia, Metabolic Syndrome X), and (iii) Psoriasis-core CP modules (Antimicrobial Peptides), Interferon α/β, IL-17A axis). Frequently recurring hubs connecting phytochemicals to these pathways included *CXCL8*, *IL6*, *PTGS2*, *MMP9*, *VEGFA*, *FLT1*, *LCN2*, *DUSP1*, *PPARG*,*PPARGC1A*, and *SOD2*, cell-cycle nodes (*CCNB1*, *CCNB2*, *CDK1*, *MKI67*, *BIRC5*, *AURKA*) linked DB terms emphasizing cell activation/movement and ML pathways capturing proliferation/repair. Collectively, the phytochemical target space is positioned to modulate dominant chemokine-cytokine-matrix-angiogenic circuitry and immunometabolic stress programs characteristic of psoriasis.

2.7 Network interaction analysis of psoriasis-associated targets through PPI

To characterize the interaction landscape among psoriasis-associated molecular targets, the five DEGs (*CCNB1, CDK1, MMP9, PTGS2, CYP1A1*) and the upstream regulator *CREB1*, along with its downstream transcriptional targets, were analyzed using the STRING database (v12.0) with a high-confidence interaction score threshold of 0.7. The interaction network from STRING, was then exported to Cytoscape and the PPI network obtained was characterized by its highly interconnected topology as seen in inflammation-mediated regulatory networks (Figure 5). (Refer to Section 3.9). The degree and betweenness scores revealed that *JUN*, *FOS*, *CREB1*, *IL6*, *CXCL8*, *PPARG*, *MMP9*, and *PTGS2* are high-degree hub proteins, denoting their crucial role in transcriptional activation, cytokine response, and metabolism. The interaction network consisted of two main regulatory pathways, those mediated by the, *AP-1* complex, (*FOS/JUN*) dimer and the *CREB1* mediated transcriptional circuit, which collectively integrated immune response signals with metabolism and stress-responsive

transcriptional regulation. This indicates that *CREB1* plays an integral regulatory role as an upstream transcriptional regulatory integrator with crucial functions in immune activation, keratinocyte proliferation, and metabolism in psoriatic lesions.

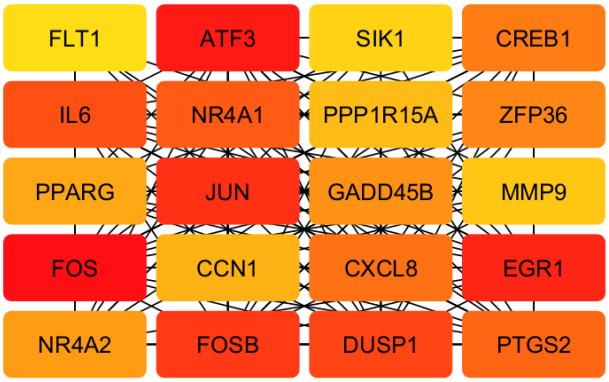

Fig. 5 Protein-protein interaction (PPI) network of psoriasis-associated targets and CREB1-regulated genes. Node color intensity corresponds to degree centrality, with red nodes indicating major hubs. Key hubs-*JUN*, *FOS*, *CREB1*, *IL6*, *CXCL8*, *PPARG*, *MMP9*, and *PTGS2*-form interconnected modules representing transcriptional activation, cytokine signaling, and metabolic regulation. Network analysis emphasise AP-1, FOS/JUN and CREB1 mediated signaling pathways that represent integrators of inflammation and cellular stress responses.

2.8 Functional enrichment of PPI network using STRING (Reactome and GO)

Analysis of functional enrichment in the protein-protein interaction network derived from the database STRING reveals the highly significant over-representation of immune and transcription signaling pathways in Reactome and Gene Ontology terms. Reactome analyses have uncovered the prominent role of the major inflammatory and stress-response signaling cascades, namely Cytokine Signaling in the Immune System, MAPK Signaling, NF-κB. Activation, IL-17 Signaling, and TNF Signaling, in addition to the Transcriptional Regulation by CREB1, all of which reflect the functional activation in psoriatic lesions of cytokine-mediated inflammation, MAPK/NF-κB stress signaling, and CREB1-associated transcription. Furthermore, the Reactome Gene Ontology Biological Process terms strongly support the prominent functional role in psoriatic lesions reflected by terms like response to cytokine stimulus, inflammation, positive regulation of transcription from the RNA polymerase II promoter, and epithelial cell proliferation. GO Cellular Component analysis was primarily composed of nucleoplasm, cytosol, transcription factor complex, and plasma membrane, which correspond to cell locations of transcription and signaling-related proteins. GO Molecular

Function categories that were significantly enriched included DNA binding transcription factor activity, protein serine/threonine kinase activity, and cytokine receptor binding, thereby reflecting the interplay between transcription, kinase activity, and cytokines in the psoriatic pathways. The full list of enriched values can be found in **Supplementary File 2**.

2.9 Construction of a tripartite network linking phytochemicals, gene targets, and pathways

To merge molecular information gleaned from PPI and enrichment analysis with phytochemical interventions, a three-way relationship was established among phytochemicals with new disease associations, gene targets, and pathways of interest in psoriasis (Figure 6). The gene targets of each phytochemicals were subjected to batch queries in the CTD database to identify their binding pathways, which were then intersected with pathways of interest in psoriasis, derived from the same sources. The intersecting pathways were retained, providing biologically significant regions of overlap demarcated by convergence at phytochemicals target sites within pathways of interest in psoriasis. The complete dataset is available in **Supplementary File 10**. ((Refer to Section 3.10)) The resulting tripartite network delineates multi-layered interactions across three biological tiers: (i) phytochemicals with new disease associations mahanine, atractylon, protopine, annomontine, taraxasterol, tricin, and tamarixetin); (ii) their validated or predicted gene targets (*CCNB1*, *CDK1*, *CREB1*, *CYP1A1*, *MMP9*, *PTGS2*), and (iii) intersecting psoriasis-associated pathways.

Specifically: *Mahanine* targets *CCNB1* and *CDK1*, mapping to *Cell Cycle*, *FoxO*, and p53 Signaling Pathways, suggesting modulation of cell proliferation and checkpoint control. *Atractylon* modulates *CREB1*, linking to metabolic and inflammatory pathways such as PI3K-Akt, AMPK, and TNF Signaling, consistent with its anti-inflammatory profile. *Protopine* and *Annomontine* act through *CYP1A1*, connecting to metabolic and xenobiotic processes, including Retinol Metabolism, Tryptophan Metabolism, and Metabolism of Xenobiotics by Cytochrome P450. *Taraxasterol* targets *MMP9*, engaging IL-17 and TNF Signaling Pathways, which are central to psoriatic inflammation. *Tricin* and *Tamarixetin* converge on *PTGS2*, influencing IL-17, NF-κB, and VGF Signaling, which govern cytokine-mediated inflammation and angiogenesis. Collectively, the findings reveal a coherent systems-level framework wherein the identified phytochemicals with new disease associations collectively modulates inflammatory, proliferative, and metabolic signaling cascades implicated in psoriasis. The integration of these compound-gene-pathway relationships highlights the potential for synergistic phytochemical combinations to restore immune and epidermal homeostasis in psoriatic conditions.

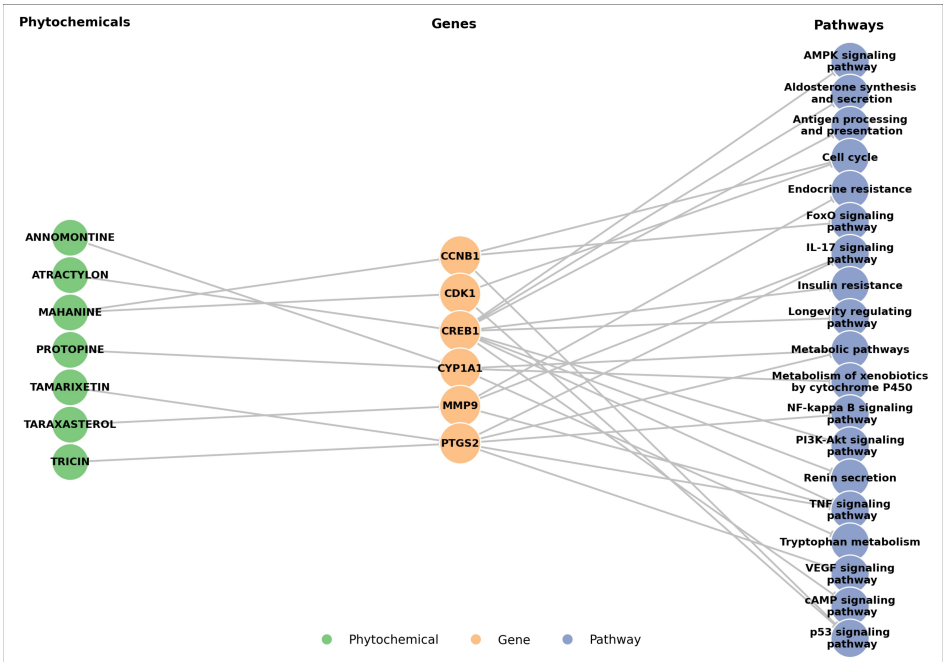

Fig. 6 Tripartite network illustrating phytochemical-gene-pathway interactions in psoriasis. The network integrates three biological layers: phytochemicals (green), their validated or predicted gene targets (orange), and psoriasis-associated pathways (blue). Edges represent experimentally supported or literature-derived associations.

3 Methods

This study applied a transcriptomic-systems biology workflow to identify and prioritize phytochemicals that may modulate psoriasis biology. An overview of the pipeline is shown in Figure 7.

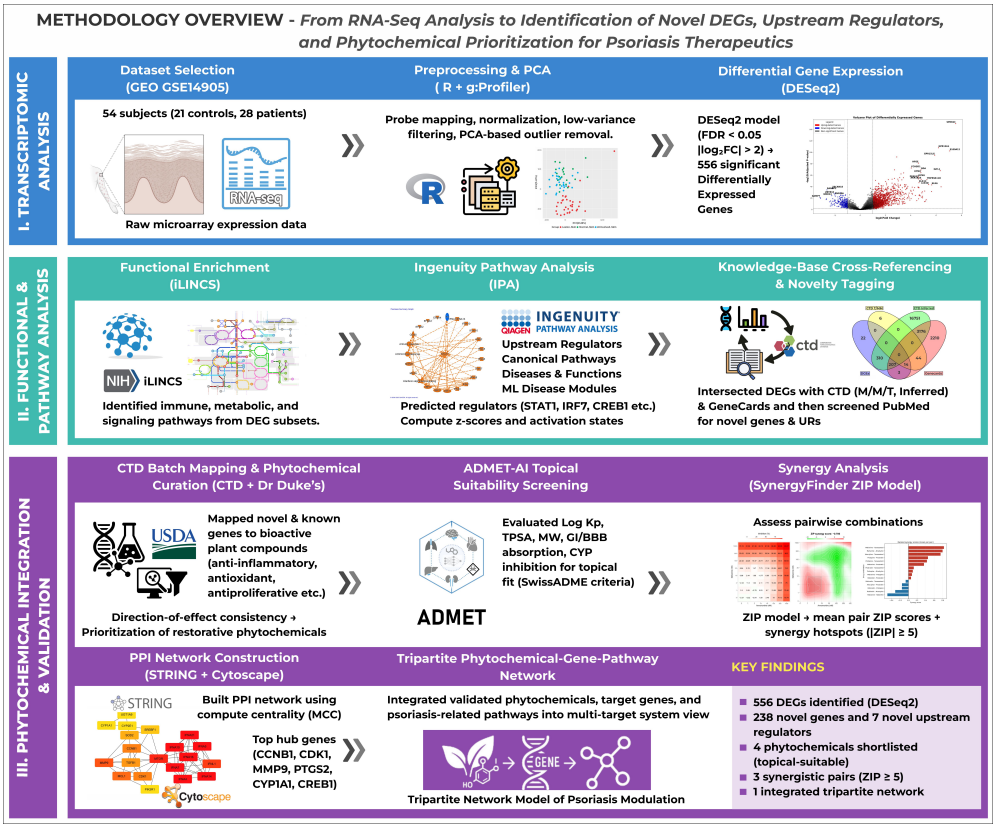

Fig. 7 Overall methodology workflow illustrating dataset selection, preprocessing, differential expression analysis, knowledge-base cross-referencing with evidence tiering, pathway and regulator analysis (iLINCS, IPA), CTD-based chemical mapping with phytochemical curation, ADMET screening for topical suitability, ZIP-based synergy analysis, and network construction/enrichment.

3.1 Data Preprocessing and Exploratory Analysis

Gene-expression data were obtained from GEO accession *GSE14905* [34] (platform: Affymetrix HGU133 Plus 2.0, GPL570), comprising *82* arrays from *54* subjects: *21* healthy controls, *28* psoriasis patients contributing matched lesional and uninvolved (non-lesional) biopsies (*56* samples), and *5* additional lesional-only biopsies from NCBI GEO [35]. Probe sets were mapped to gene symbols using current annotations for HGU133Plus2.db through g:Profiler [36]. For exploratory analysis, low-variance genes were removed, and PCA was performed on the gene-level matrix to assess clustering and detect outliers (Figure 1A). PCA identified three lesional outliers, which were excluded prior to downstream analyses[37]. Unless otherwise noted, final analyses were performed on 21 healthy controls and the remaining lesional samples.

3.2 Differential Gene Expression Analysis

Differential expression was performed using the DESeq2 package, which models count data with a negative binomial distribution [38]. Genes were considered significantly altered when they met three criteria: p-value < 0.05, adjusted p-value (FDR) < 0.05, and absolute $\log_2$ fold change $|\log_2 \mathrm{FC}| > 2$ [38, 39, 40]. A volcano plot was generated from the resulting statistics.

3.3 Knowledge-Base Cross-Referencing and Identification of New Associations

To contextualize differentially expressed genes (DEGs), we cross-referenced against psoriasis-associated genes from the Comparative Toxicogenomics Database (CTD) and GeneCards [31, 32]. CTD evidence classes were treated as "marker/mechanism/therapeutic (M/M/T)" and "inferred". Overlaps among DEGs, CTD genes, and GeneCards were computed using *Venny* [33]. Two tiers were defined *a priori* (i) new-association candidates, operationally defined as DEGs absent from CTD (inferred) and GeneCards and/or lacking PubMed evidence for psoriasis based on a standardized query (`"<GENE_SYMBOL>" AND psoriasis` in [All Fields]); and (ii) high-evidence genes, defined as overlaps among DEGs, CTD MM/T, and GeneCards. This tiering was used solely to guide downstream analyses and prioritization.

3.4 iLINCS-KEGG Pathway Enrichment

KEGG pathway enrichment via *iLINCS* [41, 42] was performed on three prespecified gene sets: (1) DEGs $\cap$ CTD inferred; (2) DEGs $\cap$ CTD inferred $\cap$ GeneCards; (3) DEGs $\cap$ CTD MM/T $\cap$ GeneCards. Default iLINCS parameters with FDR control were used. Enrichment outputs (terms, statistics, and gene memberships) were retained for downstream interpretation.

3.5 Ingenuity Pathway Analysis (IPA)

DEGs with $\log_2$ fold-change and adjusted p-values were uploaded to IPA (QIAGEN). Analyses included Upstream Regulators (UR), Canonical Pathways (CP), Diseases & Biofunctions (DB), and ML Disease Pathways (MLD) [43]. IPA leverages a large, manually curated knowledge base of molecular interactions and experimental findings, which can be used for making context-specialized predictions regarding pathway activity and regulator impact. This makes it especially useful for mapping transcriptomic signatures onto biological mechanisms and putative therapeutic targets. Table 2 outlines the analysed types and the filters used. IPA significance was assessed using overlap p-values with BH correction; predicted activation was summarized by z-scores where available. IPA URs were cross-checked against CTD (MM/T, inferred) and GeneCards, PubMed screens flagged URs with new gene-disease relationship. Predicted upstream regulators from IPA were verified with our DEGs, CTD-listed psoriasis genes, and published studies for raising a flag on regulators that have not so far been associated with psoriasis.

Table 2 Summary of IPA analysis types, their purpose, and applied filters.

IPA Analysis	Explanation	Filters Applied
Upstream Regulators	Predicts transcription factors, cytokines, and other molecules influencing psoriasis lesions.	Activation state present; Z-score > 2 or < -2; $p < 0.05$
Molecules	Highlights key DEGs as biomarkers or therapeutic targets.	Log Ratio > 2 or < -2; $p < 0.05$; Ratio > 0.02
ML Disease Pathways	Identifies disease-specific pathways relevant to psoriasis pathology.	$-\log(p) > 1.3$
Diseases and Functions	Links DEGs to inflammation, immune activation, and cell proliferation in psoriasis.	$p < 0.05$; Activation state present; Z-score > 2 or < -2

3.6 CTD Batch Mapping and Phytochemical Curation

Chemical-gene interaction records were retrieved from CTD using batch queries for both tiers (new-association candidates and high-evidence genes). Retrieved chemicals were filtered against Dr. Duke's Phytochemical and Ethnobotanical Database to retain compounds with psoriasis-relevant bioactivities (antimicrobial, anti-inflammatory, antiproliferative, antioxidant, anti-angiogenic, antipruritic) [44]. For each phytochemical-gene pair, reported molecular effects (e.g., inhibition or activation of the target; increase or decrease in mRNA/protein expression) were compiled. Phytochemicals were prioritized based on *direction-of-effect consistency*, defined as inhibition of upregulated targets or restoration/activation of downregulated targets. Downstream analyses focused on two tiers: (i) phytochemicals interacting with genes showing new gene-disease associations, and (ii) phytochemicals interacting with high-evidence psoriasis genes. To operationalize this prioritization workflow, the following steps were executed:

1. Classify genes lacking prior psoriasis evidence (PubMed screen with standardized query) as new-association candidates.
2. Map IPA Canonical Pathways, Diseases & Biofunctions, and ML Disease Pathways to gene tiers and associated phytochemical targets.
3. Develop regulatory networks among tiered genes, phytochemicals, and enriched pathways. The prioritization criteria included anti-inflammatory and antioxidant activities with uniform molecular direction and pathways.

Prioritization emphasized anti-inflammatory and antioxidant profiles supported by consistent molecular directionality and pathway relevance.

3.7 ADMET-AI Topical Suitability Screening

Shortlisted phytochemicals were evaluated in *ADMET-AI* [45] for molecular weight, consensus logP, TPSA, HBD/HBA, predicted skin permeability (Log Kp), BBB permeability, GI absorption, and cytochrome P450 inhibition profiles. Suitability was assessed against a topical filter adapted from SwissADME [46] (Table 3), prioritizing low BBB permeability, acceptable skin permeability/retention, and minimal

CYP liabilities. Strict criteria was adjusted for high-value leads in the context of low-percentage (< 1-2%) dermal use and advanced carriers (e.g., nanoemulsions)[47].

Table 3 Filtering attributes for phytochemical suitability in topical formulations.

Attribute	Preferred Range/Value	Rationale
Strict Filters		
Log Kp (skin permeability)	< -5.0 cm/s	Better skin retention ability and reduced systemic absorption
TPSA (Topological Polar Surface Area)	20-120 $Å^2$	Balances skin penetration and aqueous solubility
Solubility class, categorized on the basis of ESOL, ALOGPS, and Silicos-IT, should have, at the very least, "Soluble" and "Moderately soluble" properties in order to avoid the need for solubilizers.		
GI Absorption	Low	Minimizes risk of systemic absorption from skin
BBB Permeant	No	Avoids unintended CNS effects from topical use
CYP Inhibitors (esp. CYP3A4, CYP1A2)	Preferably No	Reduces risk of drug interactions and systemic liabilities [48]
Relaxable Filters (for low-percentage use <1-2%)		
Molecular Weight (MW)	< 500 Da	Favorable for dermal penetration. - Exceptions may be permitted, in cases where there is high bioactivity.
# Lipinski Rule Violations	≤ 1	Acceptable in topical drugs intended to have low systemic absorption.
Consensus LogP	< 5.5	High logP acceptable if other filters are met
Synthetic Accessibility	< 6	Easier formulation, although this parameter isn't essential when dealing with bio-organic chemistry.

3.8 In Silico Synergy Analysis

The pairwise pharmacodynamic effects among the short-listed phytochemicals were analyzed using the SynergyFinder tool with the zero interaction potency (ZIP) reference model [49, 50]. The dose-response matrix was created for each pair of compounds over predetermined concentrations, in nanomolar units (nM), and the matrix was

normalized in terms of Relative Inhibition, following the SynergyFinder platform instructions. The ZIP model combines aspects of the models proposed by Loewe and Bliss, who argued that the effect of the combination of two non-interacting agents would ideally leave the dose-response relationships of each other unperturbed, and that the effect would simply be the arithmetic sum. Deviations of the experimentally observed response surface from this theoretical non-interaction surface are quantified as ZIP synergy scores-positive values indicating synergy and negative values indicating antagonism. ZIP scores were computed for each concentration pair to generate two-dimensional synergy landscapes and aggregated into mean pairwise ZIP scores for overall comparison. Regions with $|\text{ZIP}| \geq 5$ were defined as synergy hotspots. These were subsequently used to identify synergistic or antagonistic concentration zones, and mean ZIP scores across all pairs were rank-ordered to prioritize the most cooperative interactions.

3.9 Protein-Protein Interaction (PPI) Network and Functional Enrichment

Protein-protein interaction data for selected gene targets and the upstream regulator, including its associated DEGs, were retrieved from STRING v12.0 [51] using a high-confidence threshold (score $\geq$ 0.7). The resulting network was imported into Cytoscape v3.9.1 [52] for visualization and topological analysis. Node centrality was quantified using cytoHubba [53] with Maximal Clique Centrality (MCC) as the primary ranking metric, and degree or betweenness as secondary measures. Functional enrichment (Reactome and GO BP/CC/MF) was performed through STRING using FDR-adjusted $p < 0.05$ to identify overrepresented biological processes and pathways.

In this context, the network is represented mathematically as:

$$G = (V, E)$$

where:

- V is the set of genes (nodes)
- E is the set of interactions (edges) derived from STRING

Centrality score for node v was calculated using the Maximal Clique Centrality (MCC):

$$\text{MCC}(v) = \text{Maximal Clique Centrality of } v$$

3.10 Tripartite Phytochemical-Gene-Pathway Network

We integrated (i) shortlisted phytochemicals, (ii) their validated/predicted gene targets (CTD and curated literature), and (iii) psoriasis-relevant pathways (CTD and literature) into a tripartite network. Overlapping pathways were retained to reflect disease-relevant intersections. We defined G as the set of genes and C as the set of

compounds. An interaction matrix M with entries of 0 or 1 was constructed such that:

$$M_{gc} = \begin{cases} 1 & \text{if gene } g \text{ interacts with phytochemical } c \\ 0 & \text{otherwise} \end{cases}$$

4 Discussion

Psoriasis is increasingly recognised as a systems-level disorder in which canonical cytokine pathways are intertwined with antiviral, metabolic, neuronal and chronobiological programmes to drive chronic inflammation and epidermal hyperproliferation. In this study, we combined differential gene expression, multi-layered pathway enrichment, network analysis and chemical-gene interaction mapping with ADMET and in silico synergy profiling to move from a descriptive lesional transcriptome towards a mechanistic and intervention-focused framework. Collectively, the findings aligns toward: (i) an interferon-centred, immunometabolic view of psoriasis, (ii) a compact set of transcriptional and matrix hubs, (iii) multi-target phytochemical modulation and rational combinations, and (iv) a refined disease model with translational implications.

4.1 Interferon-centred, antiviral and immunometabolic reprogramming

Across enrichment layers, psoriatic lesions were characterised by a superposition of inflammatory, antiviral and metabolic programmes, rather than a purely IL-17/TNF-driven cytokine signature. Classical pathways such as IL-17, TNF and Toll-like receptor signalling, which underpin keratinocyte activation and leukocyte recruitment in psoriasis, were recovered as expected [54, 55, 56]. Their coexistence with antiviral and pattern-recognition modules (including interferon α/β signalling and nucleic-acid sensing pathways) supports a model in which lesional skin behaves as if chronically exposed to viral or microbial danger cues [57, 58, 59]. This is in line with the well-documented overexpression of antimicrobial peptides and interferon-stimulated genes in psoriatic plaques [60]. A key conceptual advance from our analysis is the prominence of type I/III interferon regulators and cGAS/MAVS-like upstream sensors within the IPA network, including several interferon subtypes not previously highlighted in psoriasis [61, 62]. Their predicted activation suggests that subtle differences in interferon composition could modulate plaque behaviour, disease severity and response to biologics, even against a background of shared IL-23/IL-17 wiring. The IPA-derived biological functions-antiviral response, antimicrobial response, interferon signalling-must therefore be viewed not as incidental "background noise" but as integral components of the psoriatic microenvironment. Equally important is the consistent enrichment of metabolic and endocrine axes alongside inflammatory pathways. Insulin signalling and insulin resistance, steroid hormone-related pathways and cardiometabolic modules such as NAFLD and AGE-RAGE signalling fit with epidemiological links to obesity, diabetes, fatty liver disease and accelerated vascular ageing in psoriasis [63, 64, 65]. The appearance of longevity-regulating pathways suggests that

chronic inflammatory and oxidative stress may push epidermal and vascular compartments towards an "inflammaging" like state. Taken together, these signals support an immunometabolic view of psoriasis in which interferon and IL-17/TNF axes are tightly coupled to metabolic stress, endothelial activation and systemic comorbidities, rather than operating in isolation.

4.2 Network hubs and CREB1/AP-1 circuits at the crossroads of inflammation and metabolism

Projecting the lesional signature onto a STRING-Cytoscape network condensed the complexity of individual DEGs into a small set of hubs centred on AP-1, CREB1, inflammatory cytokines and immunometabolic mediators. This pattern is consistent with an inflammatory network that is organised around a few high-connectivity nodes rather than a diffuse, evenly distributed architecture. AP-1 components (*JUN*, *FOS*/*FOSB*) and CREB1 emerged as key transcriptional integrators. Prior experimental work has shown that AP-1 in dendritic cells promotes IL-23 and chemokine production which sustains psoriatic inflammation, while keratinocyte differentiation and activation depend on coordinated Fos/Jun activity [66, 67]. CREB1, in turn, is known to integrate survival, stress and immediate early gene programmes in skin immune cells [68]. These analyses can be extended by network and GO/Reactome enrichment, which illustrate that these transcription factors are nodes at the crossroads of cytokine signaling, MAPK/NF-$\varkappa$B signaling, and metabolic control, linking inflammatory signals to genes that control growth, redox stress, angiogenesis, and lipid homeostasis [69, 70, 71]. Matrix-angiogenic and immunometabolic network nodes, such as *MMP9*, *VEGFA*/*FLT1*, *PPARG* and *PTGS2*, further highlight the incorporation of both matrix remodeling and metabolism into the inflammatory crossroads. MMP9 and VEGFA/FLT1 are well recognised as mediators of dermal remodelling and psoriatic neovascularisation [72, 73], while PPARγ and COX-2 link lipid and eicosanoid pathways to cytokine amplification and keratinocyte behaviour [74, 75]. The fact that these proteins appear as central nodes-instead of peripheral add-ons-supports the idea that vascular and metabolic changes are core features of psoriatic circuitry. Notably, some transcripts annotated as having new disease associations in our analysis were embedded within disease and function-level terms related to inflammation and cell migration. This suggests that parts of the psoriatic network remain under-characterised at the gene level, even when their functional roles (for example, leukocyte infiltration, epithelial movement) are well recognised. At the same time, we acknowledge that STRING encodes associations rather than physical binding and that graph-theoretic importance does not equate to causal necessity [76, 77, 78, 79]. Nonetheless, the convergence of network topology, enrichment signals and prior biological evidence strongly supports AP-1, CREB1, IL-6, CXCL8, MMP9, FLT1, PPARG and PTGS2 as organising centres of psoriatic signalling.

4.3 Multi-target phytochemical modulation, topical suitability and synergistic combinations

Mapping phytochemicals onto this network provided a route from systems biology to candidate interventions. The shortlisted compounds-particularly mahanine, taraxasterol, tricin, tamarixetin, annomontine, protopine and atractylon do not target single "magic-bullet" nodes but instead engage several of the hubs and pathways discussed above. This multi-target profile is conceptually attractive for a disease driven by interacting cytokine, matrix and metabolic circuits. From a mechanistic standpoint, the prioritised phytochemicals can be framed as modulators of three broad functional axes: (i) cell-cycle and proliferation (for example, mahanine influencing *CCNB1*/*CDK1*), (ii) matrix and vascular remodelling (taraxasterol acting on *MMP9* within TNF/IL-17 contexts), and (iii) inflammatory-angiogenic signalling (tricin and tamarixetin acting on COX-2/VEGF-linked modules) [80, 72, 81, 73, 75]. Atractylon's connection to CREB1 and PI3K-Akt/AMPK pathways aligns with CREB1's integrative role in immediate-early and survival responses [68], while protopine and annomontine engage xenobiotic and retinoid metabolism through CYP1A1. This pattern suggests that suitable combinations could, in principle, dampen hyperproliferation, inflammation and matrix remodelling while rebalancing metabolic and detoxification pathways.

However, not all mechanistically promising compounds are equally suitable for topical delivery. By incorporating ADMET-AI predictions, we were able to separate compounds with favourable dermal properties (notably protopine and atractylon) from those whose polarity or lipophilicity makes passive penetration across intact skin unlikely (such as tricin, tamarixetin and very lipophilic triterpenes) [63]. This does not invalidate the latter as psoriasis-relevant molecules; instead, it suggests that they may require specialised formulations (for example, nano-carriers, penetration enhancers) or may be better suited to systemic or adjunctive roles. The in silico synergy analyses strengthen the case for combinations rather than single agents. Flavonoid-alkaloid pairs frequently showed positive synergy scores, especially at asymmetric dose ratios, indicating that pathway-rich but poorly permeable polyphenols may still add value when paired with better-permeating partners. At the same time, the presence of antagonistic interactions-particularly in some atractylon-containing pairs-underscores that multi-compound formulations are not automatically beneficial and that empirical optimisation of dose and ratio will be essential. Overall, these results support a strategy in which network-informed target selection, ADMET-aware filtering and synergy-driven combination design are used together to develop phytochemical interventions tailored to psoriatic circuitry. Taken together, our findings support a model in which psoriasis is driven by an interferon-dominated, immunometabolic and transcriptionally integrated network rather than a simple "IL-17/TNF overexpression" state. Canonical cytokine pathways intersect with antiviral and antimicrobial programmes, metabolic stress (insulin resistance, NAFLD, AGE-RAGE signalling), oxidative tone and proliferative bias [63, 65]. Within this framework, AP-1 and CREB1 emerge as master transcriptional hubs that integrate cytokine, MAPK/NF-κB and metabolic inputs, controlling leukocyte chemotaxis (*CXCL8*), cytokine amplification (*IL6*), matrix remodelling (*MMP9*), angiogenesis (*VEGFA*/*FLT1*) and lipid/eicosanoid metabolism (*PPARG*, *PTGS2*) [66, 68, 72, 73, 74, 75]. Type I/III interferon modules orchestrated by STAT1

and IRFs sit atop this structure, while circadian regulators such as *BHLHE40* and tissue factor (*F3*) potentially modulate temporal aspects of plaque behaviour and thromboinflammatory risk [82, 83]. Within this architecture, the phytochemicals prioritised here-particularly protopine, atractylon and mahanine, alone or in rational combinations with selected partners-can be viewed as candidate multi-target tools to gently perturb multiple nodes rather than strongly blocking a single cytokine. Such agents would not be expected to replace biologics that directly neutralise IL-23 or IL-17, but could complement them by addressing residual inflammatory, matrix or metabolic components, or by serving as topical options in milder disease or maintenance settings. One of the limitations is that the interaction resources and in silico filters (CTD/IPA/STRING, ADMET and synergy modelling) provide mechanistic hypotheses rather than experimental confirmation. Accordingly, the shortlisted phytochemicals and their combinations represent candidates for functional validation rather than definitive therapeutic claims. Future work will prioritise testing the identified hubs and phytochemical pairs in keratinocyte-immune co-culture and organotypic skin systems, and subsequently evaluating formulation strategies for topical delivery.

5 Conclusion

This study demonstrates that psoriasis is driven by an interferon-centred, immunometabolic and transcriptional network rather than a purely cytokine-driven response. Lesional skin showed strong IL-17/TNF/TLR and HIF-1 activity together with metabolic rewiring, DNA-repair activation and a dominant type I/III interferon signature governed by *STAT1*, *IRF1*, *IRF3* and *IRF7*. PPI and functional enrichment positioned *AP-1* (FOS/JUN) and *CREB1* as central hubs linking inflammatory, metabolic and matrix-remodelling pathways through effectors such as *IL6*, *CXCL8*, *MMP9*, *FLT1*, *PPARG* and *PTGS2*. Phytochemical mapping identified seven natural compounds with mechanisms that counter these disease nodes. Further ADMET profiling prioritized protopine and atractylon, which are most suited for topical delivery, mahanine emerged as a potent but formulation-dependent scaffold. Tricin, tamarixetin and taraxasterol revealed limited standalone topical utility but facilitated important network and synergy analysis. SynergyFinder modeling identified cooperative interactions between several pairs of flavonoids and alkaloids, such as, protopine-annomontine, annomontine-tamarixetin and tricin-mahanine, indicating that multi-Target combinations could potentially offer greater activity. Taken together, this layered set of analyses offers a coherent mechanism-based short list of phytchemicals and their combinations to target the IL-17/TNF-interferon-AP-1/CREB1-COX-2/*MMP9* pathway in psoriasis. Experimental validation in keratinocyte and skin models will be essential to confirm whether these compounds, individually or in combination, can recalibrate the psoriatic network in vivo.

5.1 Reproducibility and Data Availability

Transcriptomic data analyzed in this study was obtained from the *Gene Expression Omnibus (GEO)* under accession *GSE14905* [34]. To ensure full transparency and reproducibility, all analysis scripts, processed

datasets, and supplementary outputs are openly available on GitHub at: https://github.com/sonalika07/Research_Psoriasis.

The GitHub repository contains the complete workflow codes, including:

- **ADMET AI Screening.ipynb** - Predicts physicochemical and pharmacokinetic parameters for shortlisted phytochemicals using the ADMET-AI platform, with filters for topical suitability.
- **Automatic mapping of terms in PubMed.ipynb** - Automates PubMed searches to verify associations between genes, pathways, and psoriasis-related literature evidence.
- **CP, ML, DB.ipynb** - Processes and integrates IPA outputs for Canonical Pathways (CP), Machine Learning (ML) disease modules, and Diseases & Biofunctions (DB) into structured summary tables.
- **Synergy Finder File Preparation.ipynb** - Generates pairwise dose-response matrices for SynergyFinder (ZIP model) input and exports concentration-level synergy matrices.
- **Tripartite Network.ipynb** - Constructs phytochemical-gene-pathway tripartite networks integrating CTD interactions and curated literature datasets.

All scripts are version-controlled and annotated, ensuring reproducibility of every step-from DEG identification and pathway enrichment to chemical mapping, ADMET evaluation, and synergy modeling. Random seeds were fixed for all stochastic steps, and session information is recorded alongside each script.

Supplementary information.

- **Supplementary File 1:** `S_DEGs.xlsx` - Complete list of DEGs, including $\log_2$ fold-changes and adjusted p-values used in all downstream analyses.
- **Supplementary File 2:** `S_KEGG.xlsx` - KEGG pathway enrichment results (iLINCS) for the three DEG subsets (DEGs $\cap$ CTD Inferred; DEGs $\cap$ CTD Inferred $\cap$ GeneCards; DEGs $\cap$ CTD MM/T $\cap$ GeneCards), including pathway terms and gene memberships and STRING-based functional enrichment (Gene Ontology: Biological Process, Cellular Component, Molecular Function; and Reactome pathways) for the protein-protein interaction network.
- **Supplementary File 3:** `S_UR.xlsx` - IPA upstream regulators (URs) for the DEG set, with activation z-scores, overlap p-values, and literature-evidence tiers.
- **Supplementary File 4:** `S_NG-KPC_ixns.xlsx` - Known phytochemicals targeting *novel* psoriasis-associated genes.
- **Supplementary File 5:** `S_ADMET_AI.xlsx` - ADMET-AI predicted physicochemical and pharmacokinetic properties for shortlisted phytochemicals.
- **Supplementary File 6:** `S_Synergy_scores.xlsx` - SynergyFinder outputs for all pairwise phytochemical combinations: concentration matrices for Relative Inhibition and ZIP synergy scores with corresponding dose units.
- **Supplementary File 7:** `S_CP.xlsx` - IPA Canonical Pathways significantly associated with the psoriasis transcriptomic signature.

- **Supplementary File 8:** `S_DB.xlsx` - IPA Diseases & Biofunctions enriched in the dataset, with activation-state predictions and overlapping genes relevant to psoriatic inflammation and tissue remodeling.
- **Supplementary File 9:** `S_ML.xlsx` - IPA Machine-Learning (ML) disease pathways linked to psoriasis and comorbid traits, with contributing DEGs.
- **Supplementary File 10:** `Tripartite_Network.xlsx` - Tripartite network node/edge tables linking shortlisted phytochemicals, their gene targets, and psoriasis-relevant pathways (CTD and curated literature).

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Appendix A Supplementary Results and Discussion

A.1 Gene Ontology

A.1.1 556 DEGs - Biological Processes (GO BP)

GO biological process (BP) enrichment was performed on the full 556-gene DEG set. For each enriched GO BP term, the supplementary tables provide the GO identifier, term name, overlap size, p-value, FDR, odds ratio, combined score, and contributing genes. Interpretation in the main text focuses on multi-gene categories (overlap $\geq$ 2 DEGs), but all significant single-gene categories are retained in the supplementary material **Supplementary File 2**. The GO BP analysis revealed broad multi-gene enrichment of antiviral and antimicrobial defense programs, cytokine regulation, myeloid and lymphocyte trafficking, and epidermal barrier-associated processes. Representative enriched terms include interleukin-27-mediated signaling [84], antiviral innate immune response [84], and defense response to virus [85] and to bacterium, together with multiple categories describing response to lipopolysaccharide and cellular response to molecule of bacterial origin. Additional terms capture regulation and positive regulation of tumor necrosis factor (TNF) production, interferon-β production, interleukin-10 production, and chemokine production, consistent with coordinated control of pro and anti-inflammatory cytokine networks. Chemokine-mediated signaling pathway and cellular response to chemokine reflect directed leukocyte trafficking, whereas antimicrobial humoral immune response and antimicrobial humoral immune response mediated by antimicrobial peptides highlight the contribution of epithelial antimicrobial effector molecules [86]. Epidermal barrier structure and remodeling are represented by keratinocyte differentiation [87], epidermal cell differentiation [88], epidermis development [89], skin development [90], and peptide cross-linking. Many of these processes are supported by multiple DEGs, including *OAS1*, *OAS2*, *OASL*, *MX1*, *CXCL10*, *CXCL9*, *PYCARD*, *S100A12*, *TGM1*, *TGM3*, *SPRR1A*, and *SPRR1B*, indicating integrated antiviral, inflammatory, and barrier-related signatures within lesional skin. A manual PubMed screen was used to distinguish GO BP terms that have been explicitly reported in the context of psoriasis from those that, to our knowledge, have not. The following enriched GO BP terms were not associated with psoriasis in prior PubMed-indexed reports at the time of analysis

and are therefore annotated as new GO BP-disease associations in the supplementary table: Interleukin-27-mediated signaling pathway, Antiviral innate immune response, Response to lipopolysaccharide, Cellular response to molecule of bacterial origin, Cellular response to lipopolysaccharide, Regulation of tumor necrosis factor production, Positive regulation of monocyte chemotactic protein-1 production, Positive regulation of tumor necrosis factor production, Defense response to bacterium, Regulation of type II interferon production, Defense response to fungus, Type I interferon-mediated signaling pathway, Cellular response to type I interferon, Regulation of interleukin-10 production, Positive regulation of lymphocyte activation, Regulation of interferon-beta production, Positive regulation of chemokine production, Antimicrobial humoral immune response mediated by antimicrobial peptide, Regulation of response to cytokine stimulus, Positive regulation of activated T cell proliferation, Positive regulation of T cell migration, Positive regulation of MAPK cascade, Positive regulation of interleukin-10 production, Positive regulation of interferon-beta production, Positive regulation of intracellular signal transduction, Regulation of intracellular signal transduction, Positive regulation of inflammatory response, Positive regulation of wound healing, Chemokine-mediated signaling pathway, Cellular response to chemokine, Regulation of cytokine production involved in inflammatory response, Positive regulation of interleukin-1 beta production, Cellular response to interleukin-1, Response to interleukin-1, Positive regulation of adaptive immune response, Regulation of MAPK cascade, Positive regulation of T cell proliferation, Response to type I interferon, Negative regulation of interleukin-17 production, and Angiogenesis involved in wound healing. These new BP-disease associations highlight previously under-recognised antiviral and cytokine-regulatory circuits in psoriasis.

A.1.2 556 DEGs - Molecular Function (GO MF)

GO molecular function (MF) enrichment was similarly evaluated for the 556 DEGs. For each enriched MF term, the supplementary tables list the GO identifier, term name, overlap size, p-value, FDR, odds ratio, combined score, and contributing genes. The MF analysis showed coherent signatures that complement the biological processes described above. Prominent among these were CXCR chemokine receptor binding and chemokine activity, driven by *CXCL10* and *CXCL9*, reflecting potent chemotactic signaling in lesional skin [91, 92]. Serine-type endopeptidase and serine-type peptidase activity, largely mediated by kallikreins and related proteases (*KLK13*, *PRSS3*, *KLK8*, *KLK6*), point to active proteolytic remodeling at the epidermal surface and are consistent with broader endopeptidase activity in inflammatory disease settings [93]. R-SMAD binding and RNA polymerase II-specific DNA-binding transcription factor binding (*JUN*, *FOS*, *PARP9*, *PPARGC1A*) indicate engagement of transcriptional regulators downstream of cytokine and growth factor signaling, while nuclear receptor binding connects these signatures to vitamin D receptor-mediated transcriptional control [94]. Interleukin-6 receptor binding and interleukin-1 binding (*PYCARD*, *IL36RN*) further underscore the prominence of cytokine-receptor interactions within the enriched network. In addition, multiple metal ion-binding functions—including zinc ion binding, transition metal ion binding, and iron ion binding—were enriched

(e.g., *ADAMDEC1*, *GDA*, *LCN2*, *S100A12*, *BIRC5*, *TK1*, *ACP5*), suggesting a relevant contribution of metallo-enzymes and redox-sensitive processes to psoriatic lesion biology. Receptor-level interactions such as RAGE receptor binding provide an additional mechanistic link between inflammatory, metabolic, and oxidative pathways [95]. PubMed screening showed that several of these MF terms had not been previously reported as explicitly associated with psoriasis. The following enriched GO MF categories are therefore annotated as new MF-disease associations in the supplementary tables: CXCR chemokine receptor binding, Serine-type endopeptidase activity, R-SMAD binding, Serine-type peptidase activity, Zinc ion binding, Transition metal ion binding, RNA polymerase II-specific DNA-binding transcription factor binding, Hyaluronongluco saminidase activity, Interleukin-6 receptor binding, Iron ion binding, Interleukin-1 binding, and STAT family protein binding. Together with the BP results, these MF enrichments support an integrated picture of chemokine-driven leukocyte recruitment, cytokine-receptor crosstalk, and ion- and redox-dependent enzyme activity in lesional skin. Across all analyses, the complete KEGG, Reactome, GO BP, and GO MF enrichment results—including both multi-gene and single-gene terms and the classification of each category as an established or new disease association—are provided in the supplementary tables together with full gene lists, allowing independent re-analysis and integration with other datasets.

A.1.3 179-gene subset - Biological Processes (GO BP)

GO biological process enrichment for the 179-gene subset is summarized in the BP supplementary table with GO identifier, term name, overlap size, p-value, FDR, odds ratio, combined score, and contributing genes. Compared with the broader 556-gene analysis, this refined gene set shows a shift toward processes related to metabolic regulation, hormone and steroid biosynthesis, epithelial morphogenesis, vesicle and membrane dynamics, and selected immune and developmental programs. Prominent multi-gene categories include positive regulation of glycolytic process and regulation of glycolytic process (*INSR*, *ZBTB20*), positive regulation of ATP metabolic process (*INSR*, *ZBTB20*), positive regulation of D-glucose import and transmembrane transport, and multiple related terms such as positive regulation of carbohydrate metabolic process, regulation of D-glucose import, and regulation of glycogen biosynthetic and metabolic processes (*INSR*, *ZBTB20*, *OSBPL8*, *PPP1R3B*). Together these highlight coordinated control of glucose uptake, glycolysis, ATP production, glycogen turnover, and insulin receptor-linked signalling in psoriatic inflammation [96], as well as cAMP-PKA-CREB-mediated metabolic regulation targeted by PDE4 inhibition [97]. Hormone biosynthetic process, steroid hormone biosynthetic process, androgen metabolic and biosynthetic processes, estrogen biosynthetic process, and progesterone metabolic process (genes including *HSD17B1*, *SRD5A3*, *DHRS9*) emphasize steroidogenesis and retinoid metabolism as recurring themes. Additional multi-gene BP terms capture epithelial and membrane-associated processes, including epithelium development [98], membrane organization, membrane biogenesis, phospholipid and glycerophospholipid metabolic processes (*SOX17*, *DHRS9*, *SMOX*, *SOX8*, *OSBPL8*, *ATP10B*, *SPTBN1*, *GDPD3*), protein targeting and establishment of protein localization to membrane (*RTP4*, *ZDHHC21*, *YIF1B*), and several categories

of monoatomic and inorganic anion transmembrane transport, chloride transmembrane transport, and epithelial fluid transport (*GABRP*, *SLC5A1*, *SLC26A9*, *CLIC5*). Developmental and morphogenetic signatures are represented by positive regulation of morphogenesis of an epithelium, heart development and heart morphogenesis, heart looping, embryonic heart tube morphogenesis, regulation of embryonic development, regulation of multicellular organismal development, ureter development, kidney development, and neural crest cell migration and development (genes including *SOX17*, *SOX8*, *SMOX*, *SEMA3G*, *PDLIM3*, *ADAP2*). Cell cycle and genome stability functions are reflected in sister chromatid segregation, mitotic sister chromatid segregation, mitotic nuclear division, error-prone translesion synthesis, double-strand break repair via break-induced replication, homologous recombination, and mitotic DNA replication (*CENPK*, *ZWINT*, *KIF2C*, *BRIP1*, *GINS2*, *TK1*, *POLE2*). Although the 179-gene subset is less dominated by classical inflammatory categories, several immunological and redox-linked terms emerge, including positive regulation of respiratory burst and regulation of respiratory burst (*INSR*), lymphocyte migration into lymphoid organs (*NEDD9*), regulation of myeloid leukocyte-mediated immunity and leukocyte-mediated cytotoxicity (*DNASE1L3*), regulation of αβ T cell proliferation, differentiation, and activation (including specific regulation of CD4- and CD8-positive αβ T cells, *SH3RF1*), regulation of cytokine-related processes such as regulation of glucan biosynthetic process (*PPP1R3B*), and glutathione biosynthetic and catabolic processes (*CHAC2*), which align with emerging data on oxidative stress and T cell regulation in psoriasis and its treatment [96, 99]. Further enriched terms involve positive regulation of cell motility and mesenchymal cell migration (*SMOX*, *INSR*, *SEMA3G*, *NEDD9*, *SOX8*), fat cell differentiation (*OSBPL8*, *SOX8*), smooth muscle tissue development, osteoblast proliferation, melanocyte differentiation, and multiple aspects of cardiac, mesoderm, and lateral mesoderm development (genes including *SOX8*, *SOX17*, *SMOX*, *MREG*). PubMed screening was performed to distinguish BP terms with prior explicit psoriasis associations from those that, to our knowledge, have not been previously linked to psoriasis. The following enriched terms are therefore annotated as new GO BP-psoriasis associations in the BP supplementary table: ovarian steroidogenesis (from KEGG, listed here for completeness), positive regulation of glycolytic process, chloride transmembrane transport, androgen metabolic process, steroid hormone biosynthetic process, positive regulation of morphogenesis of an epithelium, cAMP-mediated signaling, positive regulation of D-glucose import, hormone biosynthetic process, inorganic anion transmembrane transport, positive regulation of ATP metabolic process, membrane organization, regulation of glycolytic process, glutathione catabolic process, glutathione biosynthetic process, positive regulation of respiratory burst, lymphocyte migration into lymphoid organs, polyamine biosynthetic process, regulation of alpha-beta T cell proliferation, regulation of multicellular organismal development, estrogen biosynthetic process, negative regulation of keratinocyte proliferation, membrane biogenesis, regulation of CD4-positive alpha-beta T cell activation, regulation of CD8-positive alpha-beta T cell proliferation, regulation of alpha-beta T cell differentiation, positive regulation of cell motility, negative regulation of glycogen metabolic process, fat cell differentiation, glycerophospholipid metabolic process, and regulation of respiratory burst. These labels allow

the 179-gene subset to be interpreted as a bridge between psoriatic skin biology and systemic metabolic, endocrine, and developmental processes, complementing experimental models of cAMP/PKA and T cell-directed therapies in psoriasis and related inflammatory skin disease [97, 98, 96, 99].

A.1.4 179-gene subset - Cellular Component (GO CC)

GO cellular component enrichment for the 179-gene subset, reported in the CC supplementary table, highlights a characteristic localization pattern to membrane microdomains, vesicular structures, and specialized transport complexes. Enriched terms include caveolae and plasma membrane raft (*SMOX*, *INSR*, *LRP8*), indicating that several subset genes encode proteins concentrated in cholesterol-rich signaling microdomains at the cell surface, in line with prior reports implicating caveolin-1 and membrane microdomains in psoriasis severity [100]. Additional categories such as cell projection membrane (*SMOX*, *ATP6V0A4*, *SLC5A1*), cytoplasmic vesicle membrane and endosome membrane (*GRIA2*, *MREG*, *SMOX*, *INSR*, *ATP10B*, *ATP6V0A4*, *SLC26A9*), endocytic vesicle membrane (*GRIA2*, *SMOX*, *ATP6V0A4*), vacuolar membrane (*GABARAPL1*, *ATP6V0A4*), and cation-transporting ATPase complex (*ATP6V0A4*, *ATP12A*) emphasize the importance of vesicle trafficking, endocytosis, and ion transport machinery in this gene subset, consistent with emerging evidence for endosomal and mitochondrial membrane involvement in psoriatic pathogenesis [101]. Structural and nuclear components such as spectrin-associated cytoskeleton (*SPTBN1*), cortical endoplasmic reticulum (*OSBPL8*), sex chromosome and X chromosome (*PCGF5*), neuron-to-neuron synapse (*GRIA2*), and the CMG complex (*GINS2*) further support the view that this subset encodes proteins involved in both membrane architecture and nuclear replication machinery. Based on the manual literature screen, several of these CC categories, including plasma membrane raft, cell projection membrane, cytoplasmic vesicle membrane, and endocytic vesicle membrane, did not have explicit prior linkage to psoriasis and are designated as new CC-psoriasis associations in the CC supplementary table. The 179-gene subset therefore highlights specific microdomains and intracellular structures where disease-relevant signalling and trafficking may be concentrated.

A.1.5 179-gene subset - Molecular Function (GO MF)

GO molecular function enrichment for the 179-gene subset is detailed in the MF supplementary table. The most strongly enriched functions center on cAMP and kinase regulatory activities, steroid and collagen metabolism, and lipid and signaling protein binding. cAMP-dependent protein kinase inhibitor and regulator activities (*SMOX*, *PPP1R1B*) show very high odds ratios and combined scores, indicating that elements of the PKA regulatory axis are overrepresented in this subset and align with reports of cAMP-PKA pathway dysregulation in psoriatic T cell and lesional immune profiles [102]. Steroid dehydrogenase activity acting on the CH-OH group of donors with NAD/NADP as acceptor (*DHRS9*, *HSD17B1*) reflects steroid and retinoid metabolic enzymes, while sterol binding (*OSBPL8*, *SMOX*) points to lipid-binding and lipid-transport proteins. Protein tyrosine kinase binding (*CEACAM7*, *NEDD9*, *PHYHIP*) and MAP kinase scaffold activity (*SH3RF1*) suggest scaffolding and adaptor roles in

growth factor and MAPK signaling cascades. Additional functions include insulin-like growth factor II binding (*INSR*), peptidyl-proline 4-dioxygenase and procollagen-proline dioxygenase activities (*P4HA1*), adenylate cyclase binding (*TMPRSS4*), and cyclic-nucleotide phosphodiesterase activity (*PDE9A*), collectively reinforcing a theme of finely tuned control of cAMP signaling, growth factor responses, extracellular matrix remodeling, and lipid and steroid handling in line with pharmacologic modulation of PDE activity and cAMP in psoriatic epidermis [103, 97]. PubMed screening identified multiple MF terms from this enriched set that have not, to our knowledge, been previously reported as explicitly associated with psoriasis. These terms are annotated as new GO MF-psoriasis associations in the MF supplementary table and include steroid dehydrogenase activity acting on the CH-OH group of donors, NAD or NADP as acceptor; protein tyrosine kinase binding; insulin-like growth factor II binding; peptidyl-proline 4-dioxygenase activity; procollagen-proline dioxygenase activity; adenylate cyclase binding; sterol binding; and MAP-kinase scaffold activity, in addition to the cAMP-dependent protein kinase inhibitor and regulator activities. Functionally, these results suggest that the 179-gene subset links psoriatic inflammation to metabolic, extracellular matrix, and growth-factor-driven signalling axes, extending prior observations on cAMP, PDEs, and immune-mediated psoriasis biology [103, 102, 97].

A.1.6 29-gene subset - Biological Processes (GO BP)

GO biological process enrichment for the 29-gene subset (genes with new disease associations that overlap high-evidence psoriasis genes) is summarised in the corresponding BP supplementary table, which includes GO identifier, term name, overlap size, p-value, FDR, odds ratio, combined score, and contributing genes. In contrast to the broader 556-gene and 179-gene signatures, this compact subset captures a core inflammatory and stress-response programme with direct relevance to plaque biology and comorbid traits. Multi-gene BP categories prominently enriched in this subset include positive regulation of inflammatory response, regulation of cytokine production, response to cytokine, and response to lipopolysaccharide, driven by genes such as *IL6*, *CXCL8*, *TNFAIP3*, and *S100A7*, and consistent with experimental models of psoriatic keratinocyte activation and inflammatory amplification [104, 105]. Terms related to leukocyte behaviour, including neutrophil chemotaxis, leukocyte migration, and chemotaxis, reflect the essential role of chemokines and cytokines in orchestrating immune cell infiltration into lesional skin and are in line with classic and more recent work on neutrophil trafficking in psoriasis and related inflammatory settings [106, 107]. Vascular and tissue-remodelling processes are captured by angiogenesis, blood vessel development, regulation of endothelial cell proliferation, and extracellular matrix organization, consistent with the presence of *VEGFA*, *FLT1*, and *MMP9* within the subset and with prior data implicating VEGF-driven angiogenesis and endothelial activation in psoriatic plaques [108, 109, 110]. Additional categories such as response to oxidative stress, cellular response to reactive oxygen species, response to hydrogen peroxide, and regulation of apoptotic process (involving *SOD2*, *XDH*, and apoptosis-linked genes) highlight the contribution of redox imbalance and cell survival programmes, consistent with broader evidence for oxidative stress and redox-dependent signalling in

psoriatic skin [111] and with DNA-damage-responsive pathways in CARD14-driven psoriasis variants [112]. Together, these enrichments show that the 29-gene subset condenses the broader lesion-wide transcriptomic changes into a small, high-impact module linking inflammation, leukocyte trafficking, angiogenesis, and oxidative stress, with additional links to T cell regulation and lymphocyte proliferation [113, 114]. Where not previously described in psoriasis, BP terms corresponding to endothelial activation, redox-induced vascular remodelling and AGE-RAGE-like signalling contexts (for example, those involving *IL6*, *CXCL8*, and *VEGFA*) are flagged in the supplementary table as candidate new BP-psoriasis associations, consistent with the main-text observations on cardiometabolic comorbidity and glucose and lipid homeostasis [115, 116].

A.1.7 29-gene subset - Cellular Component (GO CC)

GO cellular component enrichment for the 29-gene subset, reported in the CC supplementary table, indicates that many of these core genes encode proteins localised at the interface between the extracellular environment, the plasma membrane, and key intracellular signalling hubs. Enriched categories include extracellular space, extracellular region, and secretory granule lumen, driven by soluble mediators such as *IL6*, *CXCL8*, and *S100A7*, in keeping with the prominent role of secreted cytokines, chemokines and antimicrobial factors in psoriatic plaques [104, 107]. Plasma membrane, cell surface, and receptor complex terms reflect the presence of cytokine receptors and adhesion/signalling molecules involved in immune synapse formation and endothelial activation, complementing prior structural work on keratin and junctional organisation in diseased epidermis [117, 118]. Intracellularly, terms such as cytosol, nucleoplasm, and transcription factor complex capture transcriptional regulators and oxidative-stress enzymes (e.g. *SOD2*, *PPARG*, *TNFAIP3*) that integrate upstream cytokine cues into gene expression changes. Categories related to focal adhesion and cell-substrate junction further support roles in cell migration, endothelial remodelling, and matrix interactions, and are conceptually aligned with gap-junction and membrane-contact-dependent regulation of epidermal homeostasis and response to retinoids [119]. Several of these CC terms, particularly those linking secreted inflammatory mediators with endothelial and junctional structures, are annotated as new or under-explored psoriasis associations in the CC supplementary table where no explicit PubMed evidence was found.

A.1.8 29-gene subset - Molecular Function (GO MF)

GO molecular function enrichment for the 29-gene subset is detailed in the MF supplementary table and highlights a restricted but highly disease-relevant repertoire of activities. Enriched functions include cytokine activity, chemokine activity, and growth factor activity, reflecting the presence of multifunctional mediators such as *IL6*, *CXCL8*, and *VEGFA*, and supporting their dual roles in cutaneous inflammation, vascular remodelling, and systemic metabolic disturbance [116, 120]. Cytokine receptor binding, growth factor receptor binding, and TNF receptor binding capture ligand-receptor interactions that drive downstream signalling cascades, in line with network-pharmacology analyses of cytokine/growth-factor axes in psoriasis and

with broader work on therapeutic modulation of cytokine and platelet-derived factor pathways [121, 122]. Oxidoreductase-related terms, including superoxide dismutase activity and oxidoreductase activity acting on the CH-OH group of donors (e.g. *SOD2*, *XDH*), underscore the importance of redox control within the core network and connect to established models of oxidative stress and reactive oxygen species in psoriatic skin [111]. Additional functions such as transcription factor binding, DNA-binding transcription factor activity, and ligand-activated transcription factor activity (involving, for example, *PPARG* and other nuclear regulators) point to nodes that translate extracellular cues into stable changes in gene expression, consistent with vitamin A/retinoid and ligand-regulated transcriptional programmes relevant to epidermal differentiation and inflammation [123]. Where MF terms had not been explicitly reported in psoriasis, particularly those linking cytokine/growth-factor activities with metabolic transcription factors and redox-sensitive nuclear regulators, they are annotated as new MF-psoriasis associations in the MF supplementary table. Collectively, these results reinforce the concept that the 29-gene subset encodes core effector and regulatory functions that sit at the intersection of inflammation, vascular biology, and metabolic stress.

A.2 Integrated network and upstream-regulator interpretation

Across the 556 DEGs, the 179-gene refined subset and the compact 29-gene core, the enrichment patterns and upstream-regulator profiles converge on a disease architecture where antiviral and antimicrobial defence, cytokine networks, metabolic and endocrine control, and vascular/oxidative stress signals are tightly interwoven. IPA upstream-regulator analysis highlights type I and type III interferons, mast-cell- and neuro-immune-linked receptors (e.g. *MRGPRA2A*), and multiple transcriptional and epigenetic regulators as activated controllers, whereas metabolic and developmental regulators such as *INSR*, *ESRRA*, *PCK1*, and *ARID1A* are predicted to be inhibited. STRING network topology further places AP-1 partners (*FOS*/*JUN*), *CREB1*, *IL6*, *CXCL8*, *MMP9*, *FLT1*, and PPARγ at central positions that integrate immune, barrier, angiogenic and metabolic information flows. Taken together, the 556-gene, 179-gene and 29-gene analyses move from broad lesion-wide immune and barrier signatures (556 DEGs), through a metabolically and developmentally enriched interface subset (179 genes), down to a minimal but high-impact inflammatory-vascular-oxidative module (29 genes) that overlaps established psoriasis genes and comorbidity pathways, in agreement with prior integrative views of psoriasis as a systemic, immune-metabolic disease [104, 116, 123]. These supplementary results therefore provide the mechanistic and systems-level context for the main-text findings on upstream regulators and phytochemical-gene-pathway interactions.

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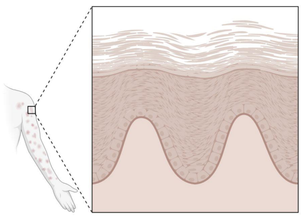
METHODOLOGY OVERVIEW - *From RNA-Seq Analysis to Identification of Novel DEGs, Upstream Regulators, and Phytochemical Prioritization for Psoriasis Therapeutics*

I. TRANSCRIPTOMIC ANALYSIS

Dataset Selection (GEO GSE14905)

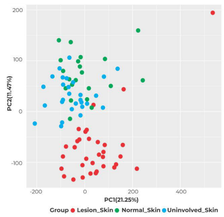
54 subjects (21 controls, 28 patients)



Raw microarray expression data

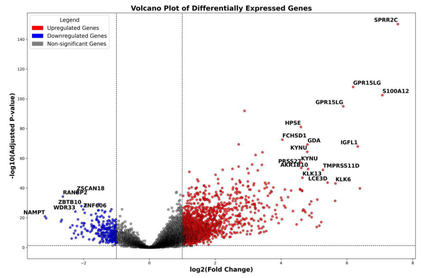
Preprocessing & PCA (R + g:Profiler)

Probe mapping, normalization, low-variance filtering, PCA-based outlier removal.



Differential Gene Expression (DESeq2)

DESeq2 model (FDR < 0.05 $|\log_2 FC| > 2$) → 556 significant Differentially Expressed Genes

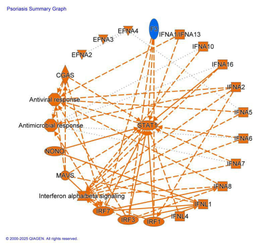


II. FUNCTIONAL & PATHWAY ANALYSIS

Functional Enrichment (iLINCS)

Identified immune, metabolic, and signaling pathways from DEG subsets.

Ingenuity Pathway Analysis (IPA)

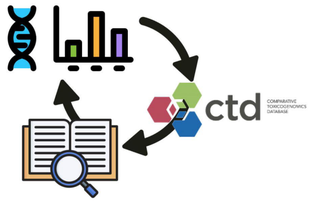


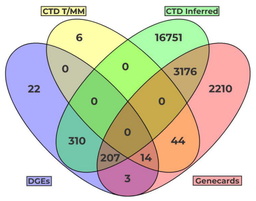
INGENUITY PATHWAY ANALYSIS

Upstream Regulators
Canonical Pathways
Diseases & Functions
ML Disease Modules

Predicted regulators (STAT1, IRF7, CREB1 etc.)
Compute z-scores and activation states

Knowledge-Base Cross-Referencing & Novelty Tagging

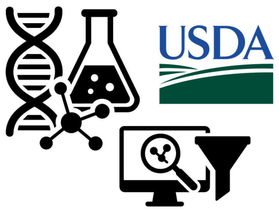




Intersected DEGs with CTD (M/M/T, Inferred) & GeneCards and then screened PubMed for novel genes & URs

III. PHYTOCHEMICAL INTEGRATION & VALIDATION

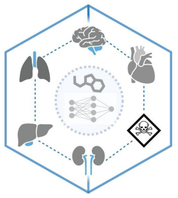
CTD Batch Mapping & Phytochemical Curation (CTD + Dr Duke's)



Mapped novel & known genes to bioactive plant compounds (anti-inflammatory, antioxidant, antiproliferative etc.)

Direction-of-effect consistency → Prioritization of restorative phytochemicals

ADMET-AI Topical Suitability Screening

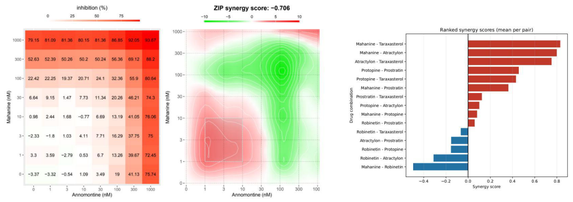


ADMET

Evaluated Log Kp, TPSA, MW, GI/BBB absorption, CYP inhibition for topical fit (SwissADME criteria)

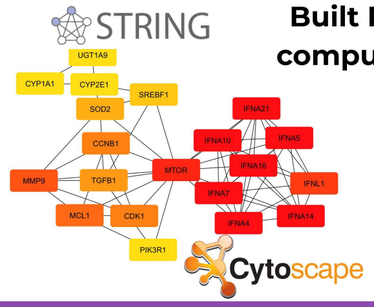
Synergy Analysis (SynergyFinder ZIP Model)

Assess pairwise combinations



ZIP model → mean pair ZIP scores + synergy hotspots (|ZIP| ≥ 5)

PPI Network Construction (STRING + Cytoscape)



Built PPI network using compute centrality (MCC)

Top hub genes (CCNB1, CDK1, MMP9, PTGS2, CYP1A1, CREB1)

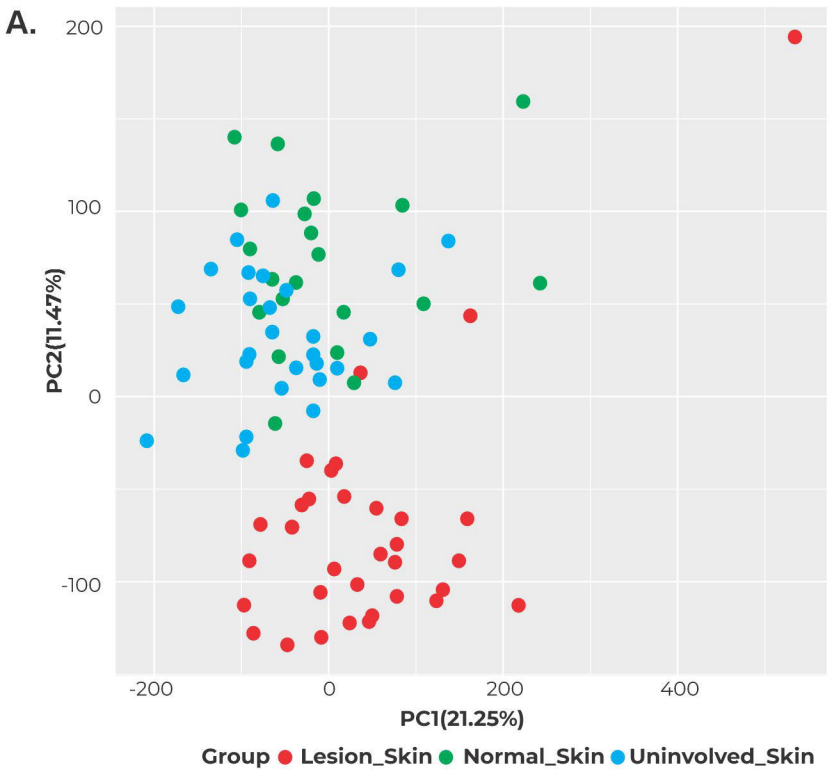
Tripartite Phytochemical-Gene-Pathway Network

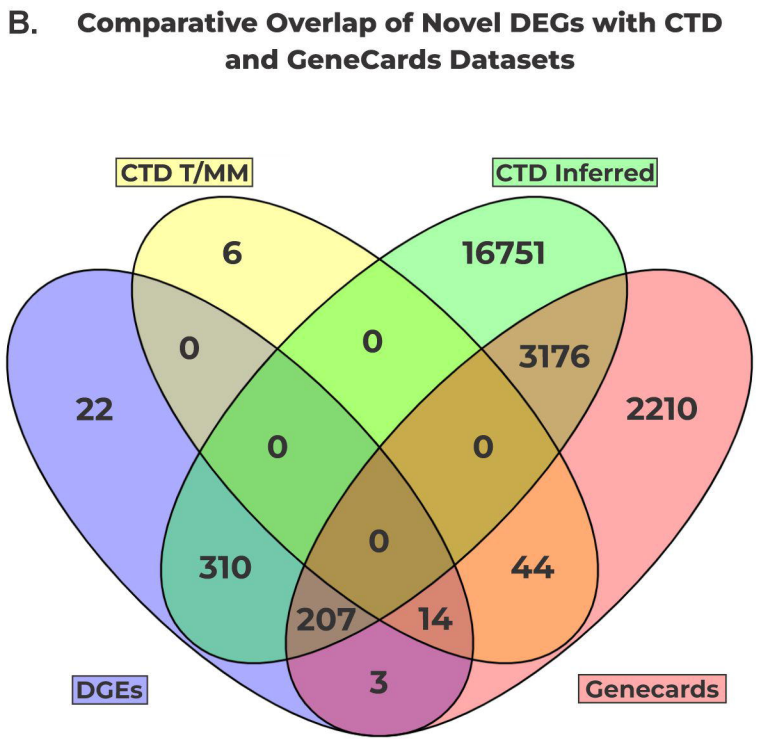
Integrated validated phytochemicals, target genes, and psoriasis-related pathways into multi-target system view

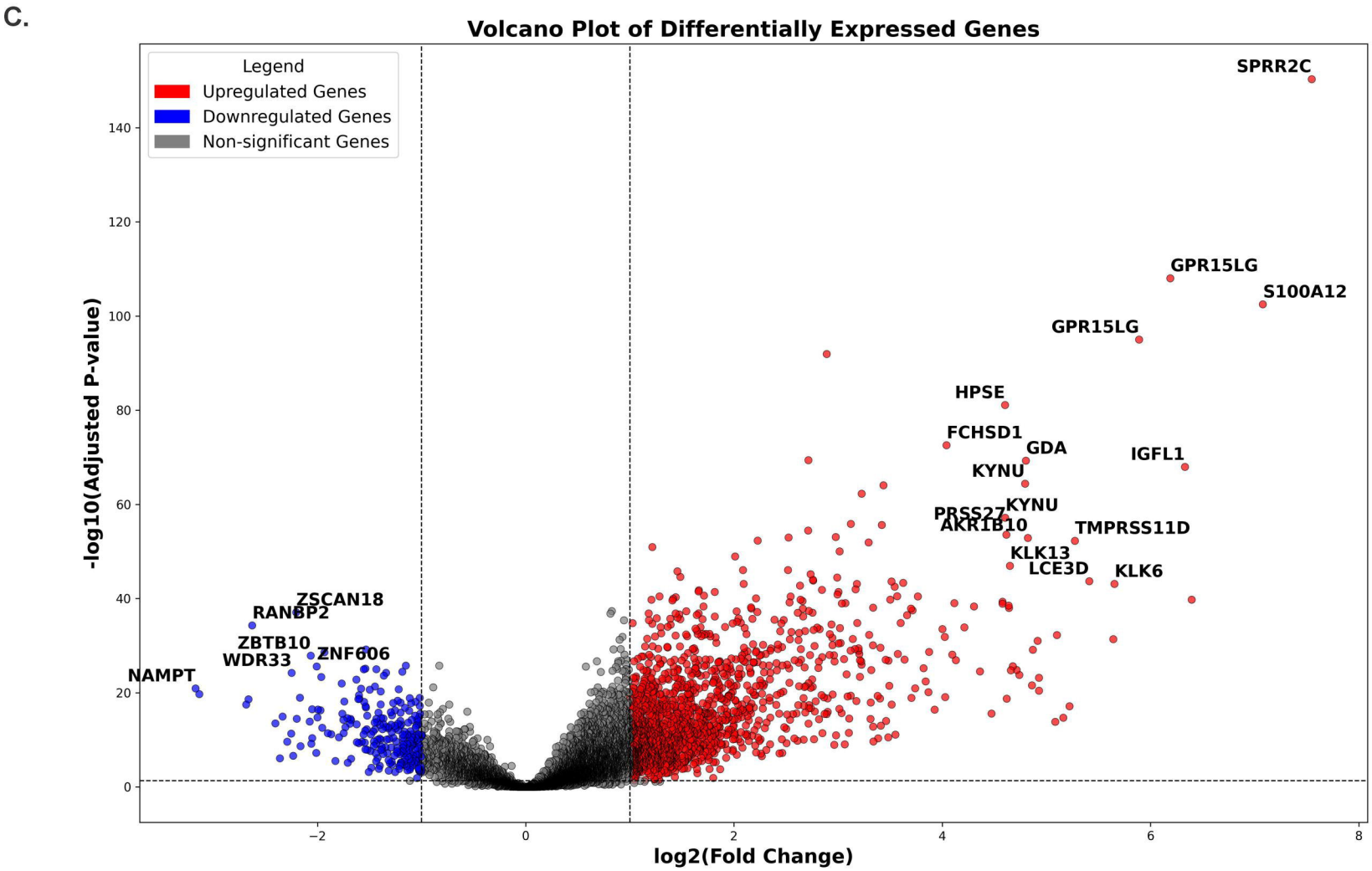
Tripartite Network Model of Psoriasis Modulation

KEY FINDINGS

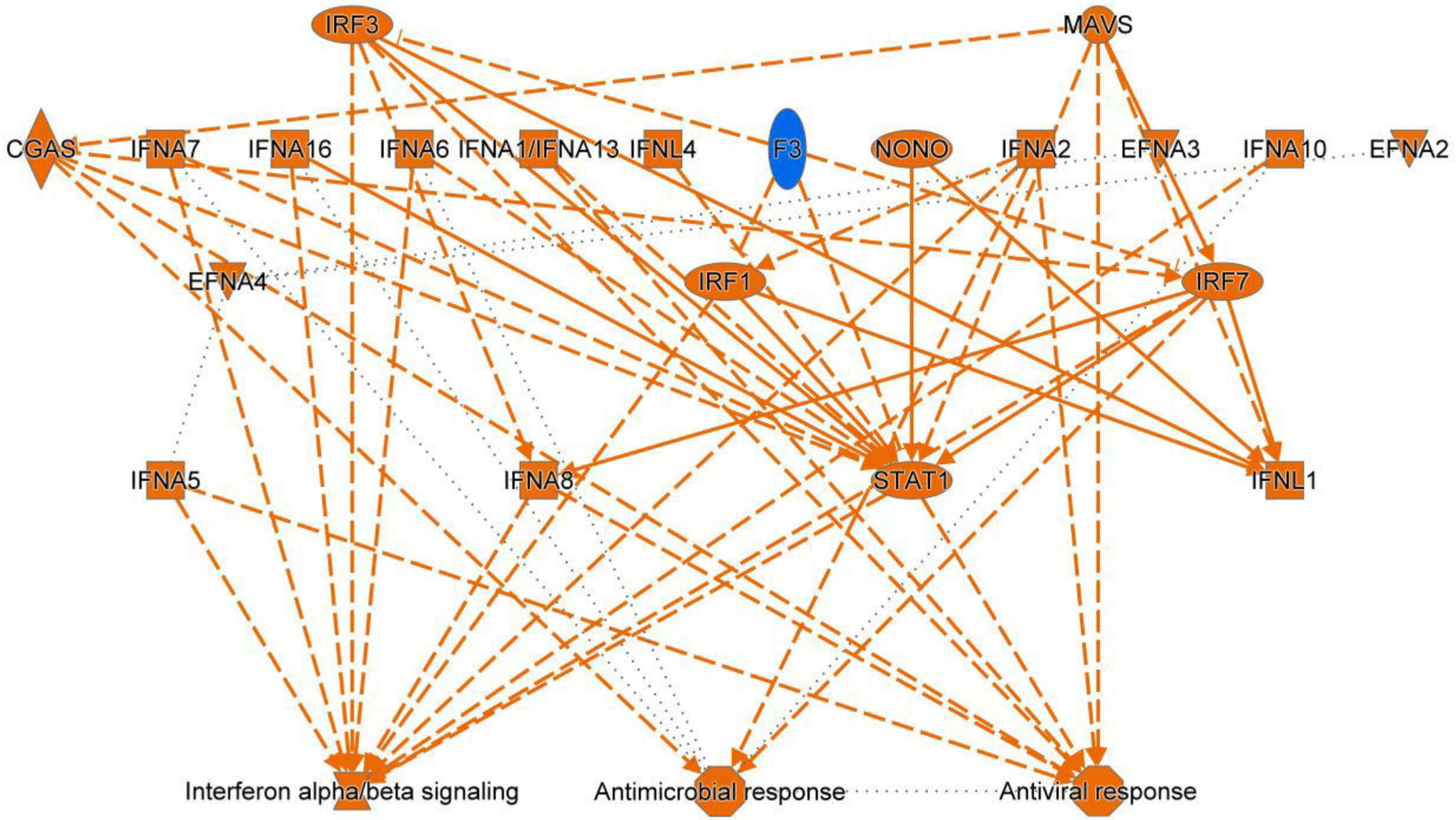
- 556 DEGs identified (DESeq2)
- 238 novel genes and 7 novel upstream regulators
- 4 phytochemicals shortlisted (topical-suitable)
- 3 synergistic pairs (ZIP ≥ 5)
- 1 integrated tripartite network


A.
200
100
0
-100
PC2(11.47%)
-200
0
200
400
PC1(21.25%)
Group Lesion_Skin Normal_Skin Uninvolved_Skin


B.
Comparative Overlap of Novel DEGs with CTD and GeneCards Datasets
CTD T/MM
CTD Inferred
DGEs
Genecards
6
16751
22
2210
0
0
3176
0
0
0
310
44
207
14
3


C.
Volcano Plot of Differentially Expressed Genes
Legend
Upregulated Genes
Downregulated Genes
Non-significant Genes
-log10(Adjusted P-value)
log2(Fold Change)
SPRR2C
GPR15LG
S100A12
GPR15LG
HPSE
FCHSD1
GDA
IGFL1
KYNU
KYNU
PRSS27
AKR1B10
TMPRSS11D
KLK13
LCE3D
KLK6
ZSCAN18
RANBP2
ZBTB10
ZNF606
WDR33
NAMPT

Psoriasis Summary Graph



Graphical Summary Legend

Predicted Activity

- Predicted activation
- Predicted inhibition

Relationships between Nodes

- Leads to activation
- Leads to inhibition
- Inferred relationship
- Indirect interaction
- Direct interaction

- Cytokine
- Other
- Transcriptional Regulator
- Transmembrane Receptor
- Kinase
- Function
- Canonical Pathway
- Enzyme

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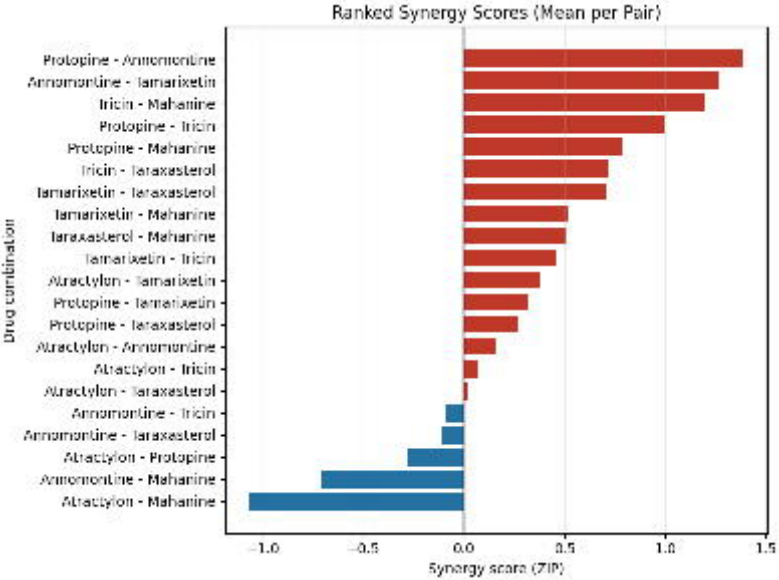
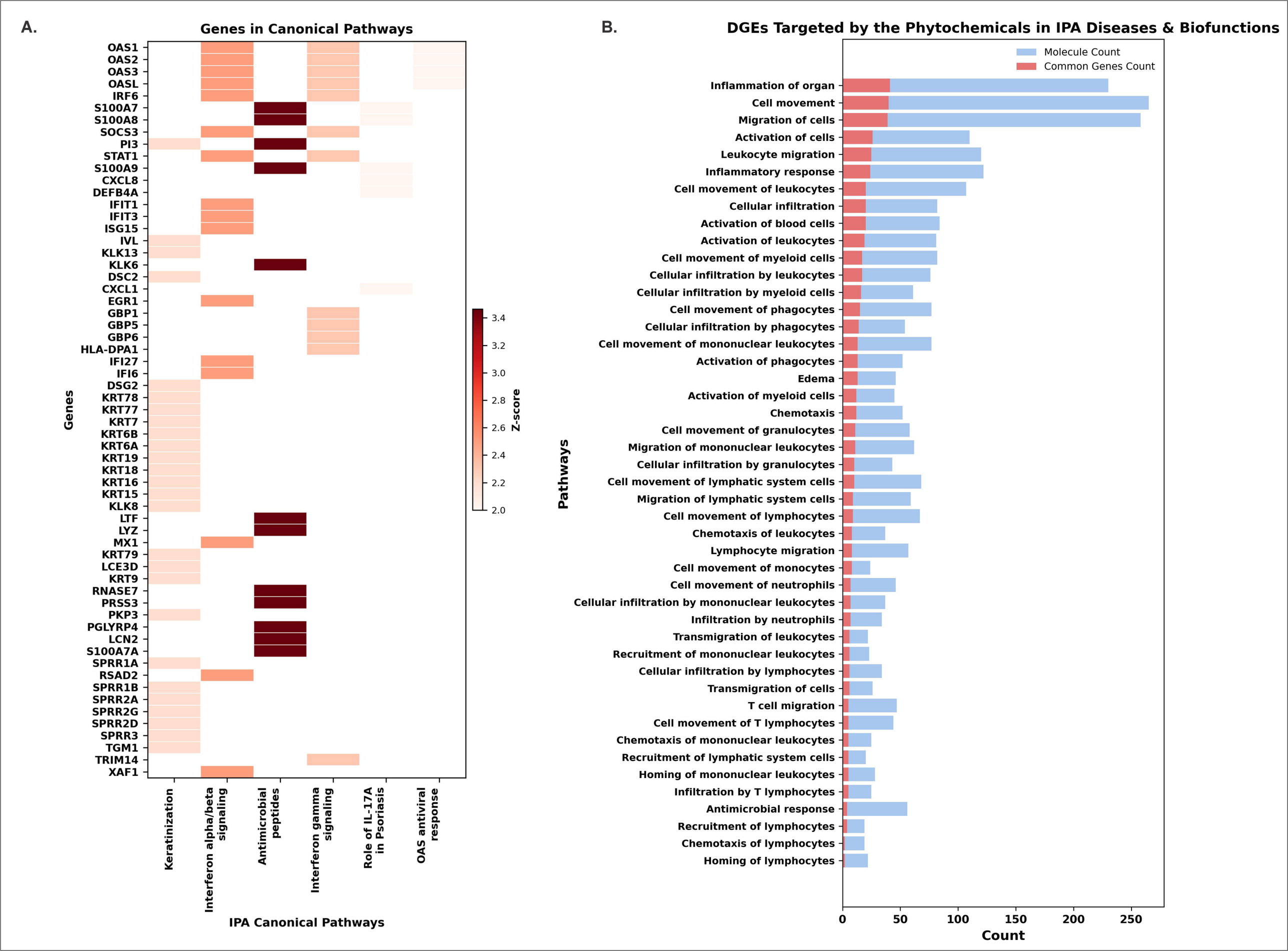
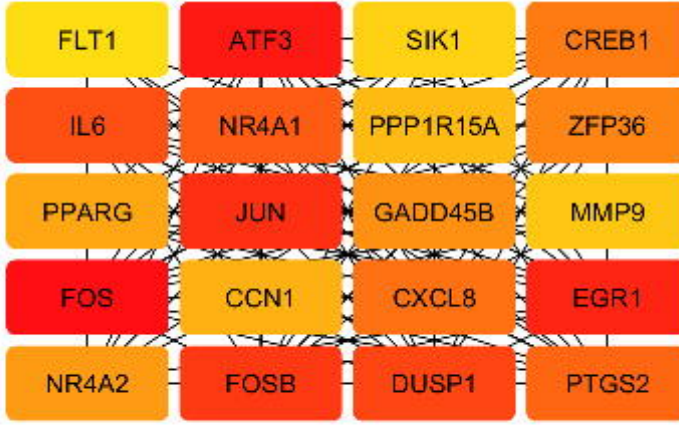
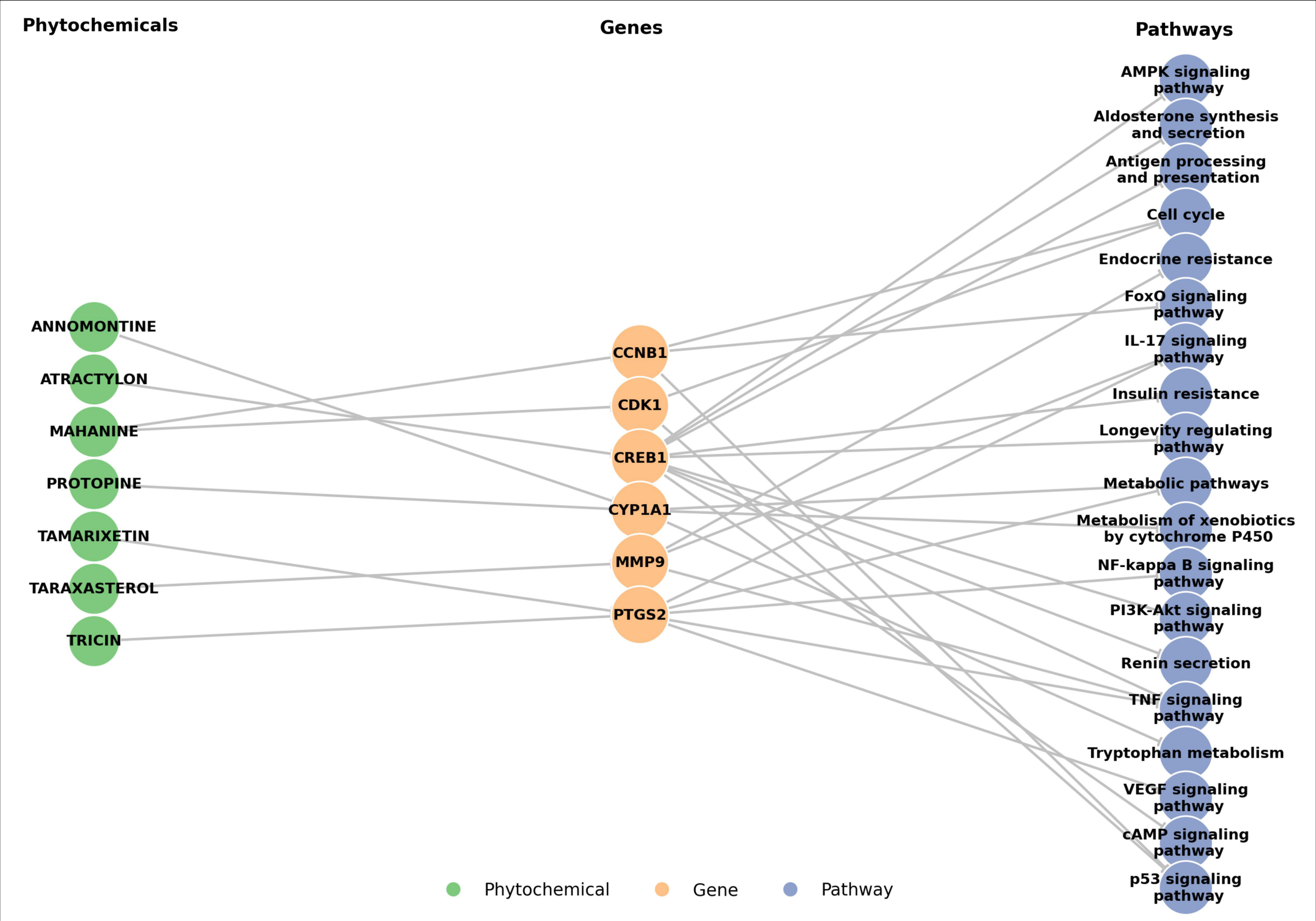

Ranked Synergy Scores (Mean per Pair)
Protopine - Ammorontine
Ammorontine - Tamarixetin
Tricin - Mahanine
Protopine - Tricin
Protopine - Mahanine
Tricin - Taraxasterol
Tamarixetin - Taraxasterol
Tamarixetin - Mahanine
Taraxasterol - Mahanine
Tamarixetin - Tricin
Atractylon - Tamarixetin
Protopine - Tamarixetin
Protopine - Taraxasterol
Atractylon - Ammorontine
Atractylon - Tricin
Atractylon - Taraxasterol
Ammorontine - Tricin
Ammorontine - Taraxasterol
Atractylon - Protopine
Ammorontine - Mahanine
Atractylon - Mahanine
Drug combination
−1.0
−0.5
0.0
0.5
1.0
1.5
Synergy score (ZIP)


A.
Genes in Canonical Pathways
Genes
OAS1
OAS2
OAS3
OASL
IRF6
S100A7
S100A8
SOCS3
PI3
STAT1
S100A9
CXCL8
DEFB4A
IFIT1
IFIT3
ISG15
IVL
KLK13
KLK6
DSC2
CXCL1
EGR1
GBP1
GBP5
GBP6
HLA-DPA1
IFI27
IFI6
DSG2
KRT78
KRT77
KRT7
KRT6B
KRT6A
KRT19
KRT18
KRT16
KRT15
KLK8
LTF
LYZ
MX1
KRT79
LCE3D
KRT9
RNASE7
PRSS3
PKP3
PGLYRP4
LCN2
S100A7A
SPRR1A
RSAD2
SPRR1B
SPRR2A
SPRR2G
SPRR2D
SPRR3
TGM1
TRIM14
XAF1
Keratinization
Interferon alpha/beta signaling
Antimicrobial peptides
Interferon gamma signaling
Role of IL-17A in Psoriasis
OAS antiviral response
IPA Canonical Pathways
Z-score
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
B.
DGEs Targeted by the Phytochemicals in IPA Diseases & Biofunctions
Molecule Count
Common Genes Count
Pathways
Inflammation of organ
Cell movement
Migration of cells
Activation of cells
Leukocyte migration
Inflammatory response
Cell movement of leukocytes
Cellular infiltration
Activation of blood cells
Activation of leukocytes
Cell movement of myeloid cells
Cellular infiltration by leukocytes
Cellular infiltration by myeloid cells
Cell movement of phagocytes
Cellular infiltration by phagocytes
Cell movement of mononuclear leukocytes
Activation of phagocytes
Edema
Activation of myeloid cells
Chemotaxis
Cell movement of granulocytes
Migration of mononuclear leukocytes
Cellular infiltration by granulocytes
Cell movement of lymphatic system cells
Migration of lymphatic system cells
Cell movement of lymphocytes
Chemotaxis of leukocytes
Lymphocyte migration
Cell movement of monocytes
Cell movement of neutrophils
Cellular infiltration by mononuclear leukocytes
Infiltration by neutrophils
Transmigration of leukocytes
Recruitment of mononuclear leukocytes
Cellular infiltration by lymphocytes
Transmigration of cells
T cell migration
Cell movement of T lymphocytes
Chemotaxis of mononuclear leukocytes
Recruitment of lymphatic system cells
Homing of mononuclear leukocytes
Infiltration by T lymphocytes
Antimicrobial response
Recruitment of lymphocytes
Chemotaxis of lymphocytes
Homing of lymphocytes
0
50
100
150
200
250
Count


FLT1
ATF3
SIK1
CREB1
IL6
NR4A1
PPP1R15A
ZFP36
PPARG
JUN
GADD45B
MMP9
FOS
CCN1
CXCL8
EGR1
NR4A2
FOSB
DUSP1
PTGS2


Phytochemicals
Genes
Pathways
ANNOMONTINE
ATRACTYLON
MAHANINE
PROTOPINE
TAMARIXETIN
TARAXASTEROL
TRICIN
CCNB1
CDK1
CREB1
CYP1A1
MMP9
PTGS2
AMPK signaling pathway
Aldosterone synthesis and secretion
Antigen processing and presentation
Cell cycle
Endocrine resistance
FoxO signaling pathway
IL-17 signaling pathway
Insulin resistance
Longevity regulating pathway
Metabolic pathways
Metabolism of xenobiotics by cytochrome P450
NF-kappa B signaling pathway
PI3K-Akt signaling pathway
Renin secretion
TNF signaling pathway
Tryptophan metabolism
VEGF signaling pathway
cAMP signaling pathway
p53 signaling pathway
Phytochemical
Gene
Pathway