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

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Abstract

Psoriasis is an inflammatory skin disorder driven by abnormal immune activation that promotes excessive proliferation and accelerated turnover of epidermal keratinocytes. IL-17 and TNF pathways are well known in psoriasis, but the other mechanisms that keep the disease active and link it to systemic comorbidities are not yet fully understood. A combined transcriptomic and systems biology framework was applied to map regulatory circuits in psoriatic lesions and to identify phytochemical candidates capable of multi-target modulation for topical intervention. Differential gene expression between lesional and healthy skin was analyzed, followed by pathway enrichment, upstream regulator inference, protein-protein interaction network, and chemical-gene interaction mapping. This integrative strategy revealed a transcriptional landscape dominated by type I/III interferon signaling, antiviral and antimicrobial responses, immune metabolic dysregulation, and transcriptional hubs centered on AP-1 and CREB1. Several genes and upstream regulators not previously associated with psoriasis were identified within inflammatory and cell migration-related modules, indicating unexplored regulatory layers in disease control. Network-guided chemical

prioritization and direction-of-effect filtering highlighted seven phytochemicals (mahanine, atractylon, protopine, annomontine, taraxasterol, tricin, and tamarixetin) with multi-target activity across key disease axes. ADMET-based screening suggested protopine and atractylon as favorable candidates for topical delivery, while synergy modeling supported flavonoid-alkaloid combination designs. This multi-layered approach provides mechanistically informed phytochemicals targeting the IL-17/TNF-interferon-AP-1/CREB1-COX-2/MMP9 axis in psoriasis. Experimental validation in keratinocyte and organotypic skin models will be required to determine whether these compounds, individually or in combination, can effectively restore psoriatic signaling in vivo.

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 an autoimmune disorder that extends beyond the skin [1]. It affects roughly 2-3% of the population worldwide, and it is more common among Caucasian people than among people living in Asia or Africa [2, 3]. It is associated with several comorbidities, such as inflammatory bowel disease, cardiovascular diseases, metabolic syndrome, and non-alcoholic fatty liver disease [4, 5]. As a result, quality of life for individuals with psoriasis is similar to that of other significant chronic conditions [6]. Epidemiological studies indicate two distinct peaks of disease onset, 20-30 years (early adulthood) and 50-60 years (later adulthood) [3]. Psoriasis develops through an ongoing interaction between inherited susceptibility and environmental factors such as infections, skin injury, psychological stress, and certain medications [7, 8]. At the mechanistic level, the disease develops through a network of interconnected biological processes, where inflammatory molecules released from affected skin can enter the systemic circulation and influence distant organs. This continuous 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, 9]. In parallel, at the cellular level, dendritic cells activates Th1 and Th17 lymphocytes and plasmacytoid cells that make type I interferon at the cellular level. These immune cells secrete cytokines, such as (TNF-α), interleukins 17 and 23, interferon-γ, and other mediators, which collectively promote keratinocyte hyperproliferation and perpetuate chronic inflammation [10, 11]. Over the past two decades, therapeutic strategies for moderate to severe psoriasis have shifted from nonspecific immunosuppressive agents to targeted biologic therapies that focus on individual cytokines[12]. Biologic drugs targeting TNF-α, IL-17, or members of IL-23 superfamily have demonstrated dramatic improvements in treatment response, leading to almost complete clearance in patients[7]. However, these drugs are not curative and result in recurrence following discontinuation [13]. Additionally, these drugs are associated with adverse reactions due to severe immune suppression or susceptibility to infections [13]. Most of the current psoriasis treatments act on

a small number of cytokines [8]. In contrast, 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 [14]. This wider range of altered pathways suggests that treatments should act on multiple biological processes at the same time. 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 [15, 16]. Other plant-derived compounds such as *Nigella sativa*, *Rubia cordifolia*, *Smilax china*, *Thespesia populnea*, and *Wrightia tinctoria* exhibit immune-modulatory properties, for relieving patients with psoriasis [17, 18]. Beyond these examples, various plant-derived compounds, for example, flavonoids, terpenoids, and alkaloids, modulate skin barrier homeostasis, alleviate oxidative stress, and properly control the activity of the immune system. These molecules hold great potential for managing inflammatory skin conditions such as psoriasis [19]. Flavonoids, along with 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]. To systematically bridge phytochemicals with disease mechanisms, contemporary breakthroughs in bioinformatics and network pharmacology allow for a rigorous mapping between phytoconstituents and genes related to diseases. One study showed that oleanolic acid helped treat psoriasis in an imiquimod model by targeting MAPK3, STAT3, PPARG, and PTGS2, using systems biology approaches [21]. Further, traditional plant extracts and individual compounds can be used as adjunct or maintenance therapies for chronic dermatosis with minimal adverse effects [22]. From a therapeutic delivery perspective, phytochemicals 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 contribute to modulating 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 isolation and identification of bioactive components [24, 25]. Modern computational methods now combine network pharmacology, 3D pharmacophore modeling, systems-level pathway analysis, and molecular docking to better understand how phytochemicals work in treating and managing skin inflammation [24, 26]. For example, in psoriasis, scientists have now specifically targeted beyond general anti-inflammatory properties, and Wang et al. employed network analyses, where quercetin 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 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, while in vitiligo, integration of transcriptomics and docking revealed that flavonoids from purslane target the PI3K/Akt and PPAR signaling axes to protect melanocytes. Existing computational and network pharmacology approaches have already connected transcriptomic changes with phytochemical-target relationships and ADMET screening. Building on these advances, applying these integrated frameworks specifically to psoriasis, with a focus on topical treatment, provides an opportunity to systematically prioritize candidates for translational development. Based on this rationale, the approach adopted in this study combines transcriptomic analysis with network pharmacology to widen the therapeutic scope of psoriasis. The objectives include the following: 1) validating known gene signatures for psoriasis and identifying novel differentially expressed genes and their regulatory factors. 2) explaining pathways and interaction networks underlying psoriasis biology. 3) associating psoriasis genes with phytochemicals, which are known to act on those genes and/or their corresponding pathways. 4) prioritizing multi-target natural products, designed for topical application, followed by evaluation of phytochemical interactions to identify synergy or antagonism. Through this approach, the study identifies key phytochemicals and provides a mechanistic rationale for their selection. This lays a strong foundation for future studies and the development of therapeutic strategies for psoriasis.

2 Results

To study gene expression patterns in psoriasis and identify potential multi-target phytochemical candidates, we analyzed publicly available transcriptomic data from GEO(GSE14905), including psoriatic lesional, non-lesional, and healthy skin samples. The workflow followed a structured pipeline that included differential gene expression analysis, database cross-referencing with psoriasis knowledge bases, pathway enrichment, upstream regulator analysis using IPA, phytochemical-gene mapping, ADMET-based topical filtering, synergy assessment, and protein-protein interaction network construction. The key findings from each stage of the analysis are presented below.

2.1 Identification of outliers and sample clusters through PCA

Principal Component Analysis (PCA) showed a clear separation between psoriasis and control groups, Figure 1A. Lesional samples (red) formed a distinct cluster from normal samples (green) and uninvolved samples (blue), reflecting transcriptomic differences associated with disease status. Uninvolved skin samples largely

overlapped with the healthy controls, indicating minimal transcriptomic alteration in these regions. Three lesional samples deviated from the main lesional cluster and were identified as outliers. These samples were excluded from further analyses to reduce variability in downstream results (Refer to Section 3.1).

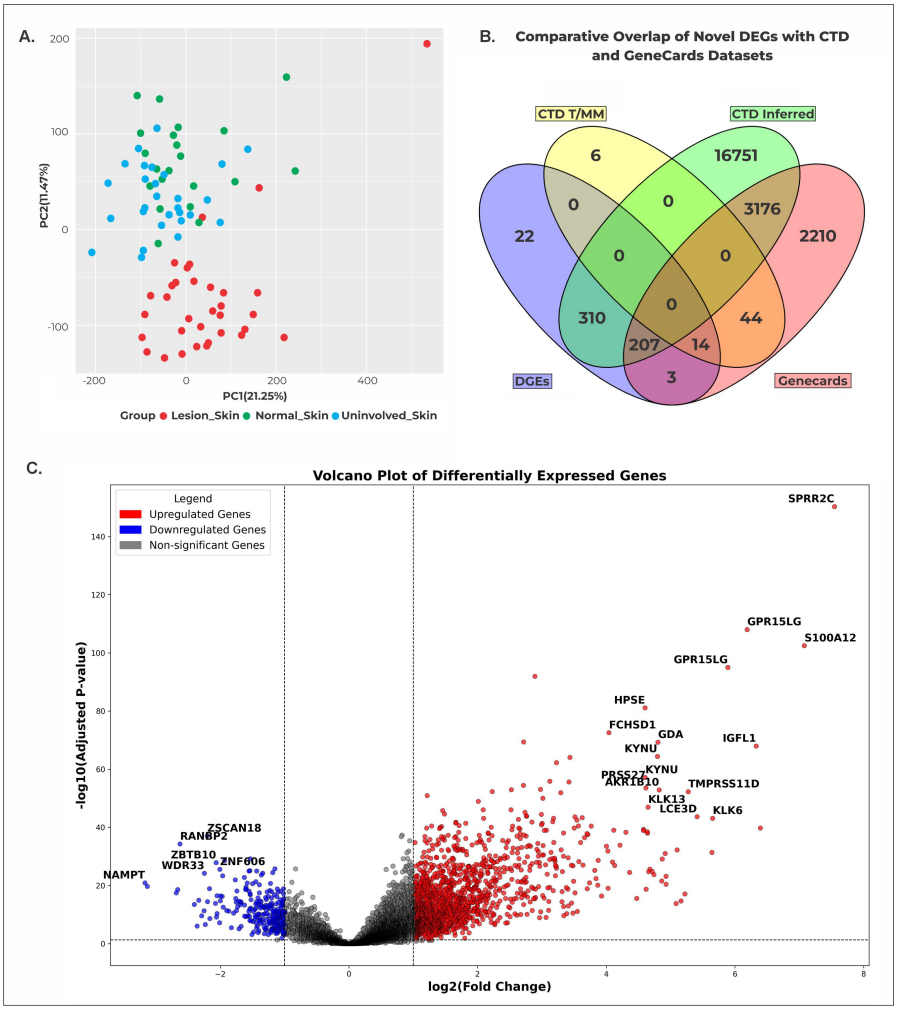

Fig. 1 Transcriptomic profiling and identification of novel gene-disease associations in psoriasis. Overview of transcriptomic analysis and gene set comparison in psoriasis. (A) PCA separation of lesional, uninvolved, and healthy skin samples. **(B)** Highlights overlap between DEGs identified in this study and genes previously associated with psoriasis in CTD and GeneCards databases. **(C)** Volcano plot of gene expression differences between lesional and normal skin.

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

Differential gene expression analysis compared lesional and healthy skin samples. A total of 556 genes showed significant expression differences, including 270 upregulated and 286 downregulated transcripts. Genes with adjusted p-value of less than 0.05 and $\log_2$ fold-change greater than 2 or less than -2 were considered statistically significant and differentially expressed. The complete DEG list is provided in Sheet 1 of Supplementary File 1. (Refer to Section 3.2). The volcano plot (Figure 1C) shows the distribution of upregulated (red) and downregulated (blue) genes. To place these DEGs in context, the 556 genes were compared with psoriasis-related genes listed in the Comparative Toxicogenomics Database (CTD) and GeneCards [29] [30]. CTD contained 20,555 psoriasis-associated genes, including 63 with marker or mechanistic evidence, one with therapeutic evidence, and 20,491 inferred associations. GeneCards listed 5,654 psoriasis-related genes. Overlap analysis using Venny identified shared and unique gene sets [31]. Two intersections were prioritized: (a) DEGs-exclusive genes, representing DEGs not present in CTD (inferred) or GeneCards (22 genes); and (b) DEGs overlapping CTD marker/mechanism/therapeutic evidence and GeneCards, representing high-confidence psoriasis genes (14 genes).

2.3 Identification of genes with new disease associations

PubMed-based literature screening was performed for the 22 DEGs-exclusive candidates. Four transcripts *DANT2, GK4P, PRSS3P1, and LINC01140* showed no prior PubMed-indexed association with psoriasis and were thus classified as genes with new disease associations. Their differential expression values were: 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). The full gene-tier classification is provided in Sheet 2 of Supplementary File 1. Additional PubMed screening identified more genes without previous psoriasis evidence. As shown in the Venn diagram (Figure 1B), among 310 genes shared between DEGs and CTD-inferred sets, 179 lacked prior PubMed association. Similarly, among 207 genes shared by DEGs, CTD-inferred, and GeneCards sets, 29 genes had no documented psoriasis link. We used these gene sets and the 14 high-evidence genes for further pathway and network analysis. This combined gene set was then used to identify phytochemicals acting on genes and new disease associations, as well as phytochemicals newly linked to known psoriasis genes. Further, we performed functional enrichment analysis on 556 DEGs through KEGG and Reactome. KEGG enrichment identified canonical inflammatory pathways, such as IL-17, Toll-like receptor, NOD-like receptor, and TNF signaling. The DEG set also showed antiviral and pattern-recognition pathway enrichment, including C-type lectin receptor signaling (*PYCARD, JUN, CLEC7A*) and the RIG-I-like receptor signaling (CXCL10, NLRX1). PubMed screening indicated that these pathways have not been previously reported in psoriasis. To refine the enrichment signal, KEGG analysis was repeated on the 179-gene subset representing DEGs with new disease associations, which gave no statistically significant results with FDR more than 0.05. The intersection of the 29 and 14-gene subsets yielded a 43-gene core

module. KEGG analysis of the core module highlighted several inflammatory pathways, such as IL-17, NOD-like receptor, and Cytosolic DNA signaling pathway. A consolidated KEGG/Reactome enrichment table is provided in Supplementary File 2.

2.4 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) highlighted key predicted regulators and their associated interaction networks. Predicted activated nodes (orange) were centered on *STAT1*, *IRF1*, *IRF3*, and *IRF7*. Upstream sensing components, including *CGAS* and *MAVS*, were connected to these regulators. Multiple interferon ligands (*IFNA* family members and *IFNL1*) were linked to functional categories annotated by IPA as Interferon alpha/beta signaling, Antiviral response, and Antimicrobial response. One node, *F3*, was predicted as inhibited (blue). The majority of connections represented inferred or indirect regulatory relationships based on the uploaded DEG expression patterns.

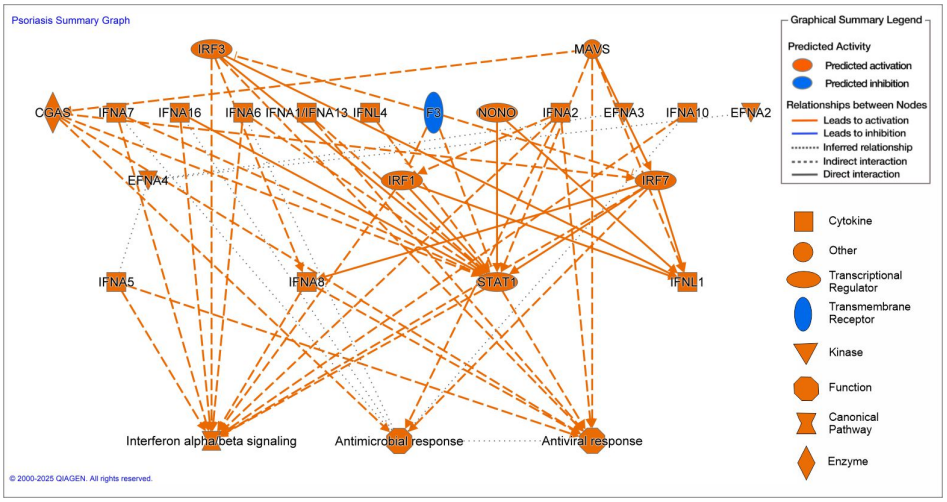

Fig. 2 Graphical summary generated by IPA showing predicted upstream regulators and functional interactions in psoriasis.

IPA Upstream Regulators: Evidence Mapping and Novel Associations

IPA identified a total of 230 upstream regulators (URs). To assess their relevance to psoriasis, all URs were cross-referenced against CTD (CTD M/M/T, inferred evidence, and GeneCards). The complete tiered mapping is provided in Supplementary File 3. PubMed screening of the IPA-exclusive regulators identified 9 URs with no prior psoriasis association: *IFNA10*, *IFNA14*, *IFNA16*, *IFNA21*, *IFNA6*, *IFNA7*, *IFNL4*, *MRGPRA2A*, and *IFNL1*. These were classified as upstream regulators with new disease associations. 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 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 regulators and regulators with new disease associations) was used in parallel with the DEG framework to guide phytochemical prioritization: (i) Mapping known phytochemicals to upstream regulators showing new disease associations, and (ii) Identifying phytochemicals newly linked to known or high-evidence URs, with emphasis on inferred relationships and direction-of-effect consistency.

2.5 Prioritization of phytochemicals through CTD-based mapping

To identify phytochemical candidates targeting psoriasis-associated genes, systematic chemical-gene mapping was performed using the CTD. Genes showing new disease associations (from both DEGs and URs) were queried in CTD through a batch search, yielding 1,569 interacting chemicals. These were compared against 6,284 psoriasis-associated chemicals already listed in CTD. Among the CTD-listed psoriasis chemicals, 6,200 had inferred evidence, 17 were classified as marker/mechanism, and 75 as therapeutic, according to CTD definitions. Comparison identified 1,296 overlapping chemicals that interacted with genes showing new disease associations while also being listed in CTD for psoriasis. These 1,296 chemicals were filtered using Dr. Duke's Phytochemical Database for relevant biological activities (anti-inflammatory, antioxidant, antiproliferative, antimicrobial, anti-angiogenic, and antipruritic), resulting in 84 phytochemicals. These compounds were listed in CTD for psoriasis only through inferred evidence and not as marker/mechanism or therapeutic agents. Across these phytochemicals, antioxidant and anti-inflammatory activities were predominant, frequently accompanied by antiproliferative and anti-angiogenic properties. Representative multifunctional compounds included *curcumin*, *quercetin*, *genistein*, and *resveratrol*. Detailed interaction data is provided in in Supplementary File 4). Next, phytochemicals targeting genes with new disease associations but not previously reported in CTD or psoriasis literature were examined; no additional compounds were identified in this category. The workflow was then repeated for known

psoriasis-associated genes (high-evidence DEGs and URs) to identify phytochemicals not previously linked to psoriasis. CTD returned 1,821 chemicals, which were filtered through Dr. Duke's database to yield 27 phytochemicals with relevant biological activities. Literature screening confirmed 13 phytochemicals as newly linked to psoriasis: annomontine, olivetol, protopine, hypaconitine, taraxasterol, atractylon, carboxyatractyloside, mahanine, bilobalide, robinetin, scutellarein, tamarixetin, and tricin. These compounds were prioritized for further analysis based on (i) consistency with direction of gene regulation, (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 evaluate the 13 phytochemicals with new disease associations, their interaction patterns with psoriasis-associated DEGs and URs were examined. The directionality of gene expression (upregulation and downregulation) was compared with the reported molecular actions of each phytochemical. Compounds predicted to counteract disease-associated expression patterns, either by suppressing overexpressed genes or restoring underexpressed genes, were prioritized, while compounds showing directionally inconsistent effects were deprioritized. Based on this screening, seven phytochemicals were prioritized: mahanine, taraxasterol, tricin, tamarixetin, annomontine, protopine, and atractylon. These compounds showed directionally consistent interactions with key psoriasis-associated targets, including (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*). The gene targets, corresponding fold changes, and reported molecular effects of these phytochemicals are summarized in Table 1. In parallel, *CREB1* was identified as an upstream transcriptional regulator targeting multiple 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. Several of these targets overlapped with the phytochemical-gene interactions identified through the DEG-based mapping.

Evaluation of shortlisted phytochemicals for topical suitability using ADMET-AI

To evaluate the topical suitability of shortlisted phytochemicals, we analyzed physicochemical and pharmacokinetic properties using the ADMET-AI platform. Parameters included molecular weight, LogP, topological polar surface area (TPSA), hydrogen bond donors and acceptors, predicted skin permeability, and toxicity indicators. ADMET profiles of all compounds are provided in Supplementary File 5. Protopine and atractylon displayed physicochemical profiles compatible with passive dermal penetration, showing moderate LogP values, lower TPSA, minimal toxicity alerts,

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).

and balanced lipophilicity. Mahanine satisfied multiple physicochemical criteria, however, its LogP value exceeded 6, indicating high lipophilicity. Annomontine showed acceptable permeability and safety parameters, with moderately elevated AMES scores. Tricin and tamarixetin exhibited high TPSA values (> 100 Å^2), indicating limited potential for passive skin penetration. Taraxasterol showed very high lipophilicity ($\log P = 8$), suggesting limited passive dermal absorption. Therefore, these compounds are not suitable as standalone topical actives but may still contribute mechanistic insights or be incorporated through specialized delivery systems. These ADMET-derived properties were used to rank phytochemicals based on dermal applicability (refer to Section 3.7).

2.6 SynergyFinder identifies phytochemical combinations with synergistic interactions

Potential interactions among shortlisted phytochemicals were evaluated in silico using the SynergyFinder platform with the ZIP reference model. Seven compounds were tested: mahanine, taraxasterol, tricin, tamarixetin, annomontine, atractylon, and protopine. Concentration-response matrices were generated for each pair, producing (i) concentration-dependent ZIP synergy score matrices and (ii) summary synergy scores including mean ZIP and most-synergistic-area scores. Filtering was applied to retain interactions with absolute ZIP scores > 5, indicating strong synergy (positive ZIP) or antagonism (negative ZIP). Tamarixetin-annomontine showed the highest synergy, with ZIP scores > 10.67 at 300 nM tamarixetin and 1 nM annomontine, and sustained synergy across 3-30 nM annomontine (ZIP 8.09-7.86), accompanied by relative inhibition of approximately 66-69%. The mahanine-tamarixetin pair displayed a ZIP score of 7.78 at 3 nM mahanine and 300 nM tamarixetin. The tricin-protopine combination showed ZIP scores of 7.51 (300/1 nM) and 6.23 (300/10 nM), with relative inhibition exceeding 70%. Taraxasterol-tamarixetin exhibited a ZIP score of 7.10 at 300/300 nM, with additional interactions showing ZIP scores > 5 across multiple dose ratios. Tricin-annomontine (ZIP = 6.51 at 300/300 nM; 5.73 at 100/1 nM) and tricin-tamarixetin (ZIP = 6.50 at 300/100 nM) also showed consistent synergistic interactions. Moderate synergy (ZIP = 5–6) was observed for mahanine-protopine and mahanine-tricin pairs. Negative ZIP scores (≤ -5) were primarily observed for atractylon-associated pairs, including tricin-atractylon and mahanine-atractylon, with minimum values reaching -8.72. Additional antagonistic interactions were identified for protopine-atractylon, taraxasterol-tricin, and mahanine-annomontine at higher or equimolar concentrations ($\geq$ 100 nM). The complete synergy matrices, including relative inhibition and ZIP scores across concentration pairs, are provided in Supplementary File 6. Mean ZIP synergy scores were computed for each phytochemical pair and visualized as a ranked bar plot (Figure 3). The highest mean ZIP scores were observed for protopine-annomontine (1.388), annomontine-tamarixetin (1.262), and tricin-mahanine (1.201). Additional pairs, including protopine-tricin and protopine-mahanine, also showed positive mean synergy scores.

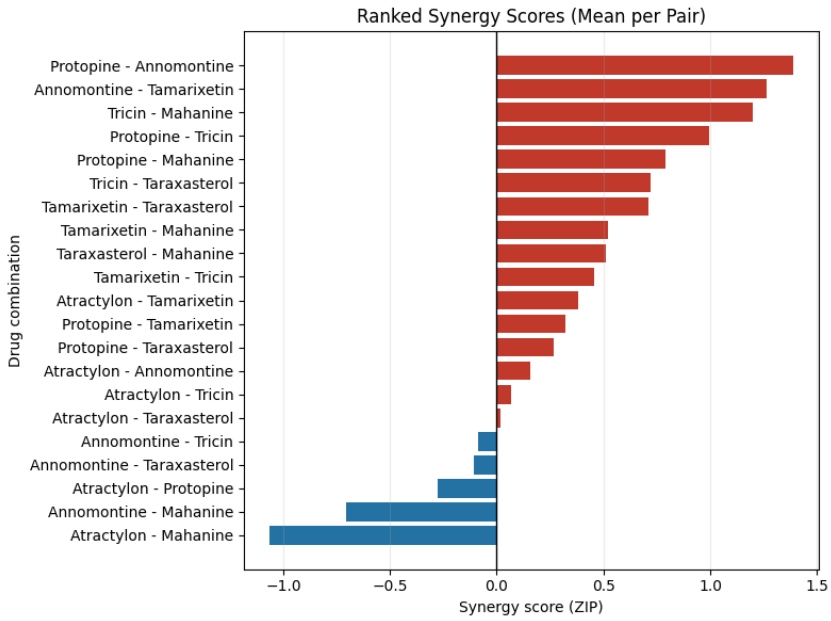

Fig. 3 Ranked ZIP synergy scores among phytochemical pairs.

Moderate synergistic interactions were observed for tricin-taraxasterol, tamarixetin-taraxasterol, tamarixetin-mahanine, and taraxasterol-mahanine, with mean ZIP scores ranging from 0.45 to 0.72. In contrast, atractylon-mahanine (-1.062), annomontine-mahanine (-0.706), and atractylon-protopine (-0.275) showed overall antagonistic effects.(Refer to Section 3.8)

2.7 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 results were examined across three knowledge layers: Canonical Pathways (CP), Diseases & Biofunctions (DB), and ML Disease Pathways (MLD). Pathway signals were cross-mapped with genes targeted by shortlisted phytochemicals with new disease associations to identify overlap between DEG modules and phytochemical target networks. A target gene set was compiled from DEGs (*CCNB1*, *CDK1*, *MMP9*, *PTGS2*, and *CYP1A1*) and the upstream regulator *CREB1* identified by IPA. Inclusion of *CREB1* expanded the target set to include downstream transcriptional networks linked to DEG regulation.

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

CP enrichment was dominated by immune-barrier and antiviral modules, including Antimicrobial Peptides, Interferon α/β Signaling, Interferon γ Signaling, Keratinization, and Role of IL-17A in Psoriasis. Key DEGs mapping to these pathways included *LCN2* (Antimicrobial Peptides), *EGR1* (Interferon α/β signaling), and *CXCL8* (IL-17A axis). The OAS Antiviral Response pathway was also enriched despite the absence of prior curated literature linking this module to psoriasis. Several genes within these enriched pathways overlapped with direct phytochemical targets or were indirectly connected through the upstream regulator *CREB1*. A pathway-level overview is shown in Figure 4A, and **Supplementary File 7** contains a list of enriched canonical pathways.

Fig. 4 Integration of IPA canonical pathway and disease/biofunction enrichment. (A) Heatmap of psoriasis DEGs across enriched IPA pathways. Darker colors indicate stronger activation. **(B)** Bar plot of IPA disease and biofunction terms linked to phytochemical-targeted genes. Blue bars show total genes and red bars show overlapping genes, highlighting inflammation and immune activity in psoriasis.

Diseases & Biofunctions (IPA): Inflammation, leukocyte trafficking and tissue remodeling

DB enrichment reflected inflammatory processes characteristic of psoriasis, with positive activation scores for Inflammation of Organ, Inflammatory Response, and

leukocyte-related functions, including Leukocyte Migration, Cell movement/migration, Cellular Infiltration, Chemotaxis, and Transmigration. Two DEGs showing new disease associations *PRSS3P1* and *LINC01140* were also represented within the DB result. *PRSS3P1* mapped to **Inflammation of Organ**, while *LINC01140* mapped to **Cell Movement**, **Migration of Cells**, and **Inflammatory Response**. A subset of enriched DB categories related to leukocyte activation, migration, homing, recruitment, cellular infiltration, and transmigration across multiple immune cell types (lymphocytes, T lymphocytes, granulocytes, neutrophils, phagocytes, and mononuclear leukocytes) lacked prior curated literature directly linking these biofunctions to psoriasis. The DB results are summarized in Figure 4B and detailed in **Supplementary File 8**. ML pathway analysis highlighted immunometabolic and comorbidity-associated themes commonly linked to 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*. The complete list of ML-derived disease and pathway annotations is provided in **Supplementary File 9**.

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

Cross-mapping phytochemical targets with CP, DB, and ML outputs showed convergence on: (i) inflammatory trafficking and activation pathways (DB: Inflammation of Organ, Inflammatory Response, Leukocyte Migration, Cellular Infiltration); (ii) oxidative stress and immunometabolic pathways (ML: Oxidative Stress, Insulin Resistance, Hypertriglyceridemia/Hyperglyceridemia, Metabolic Syndrome X); and (iii) psoriasis-associated canonical modules (CP: Antimicrobial Peptides, Interferon α/β Signaling, IL-17A axis).

Genes recurring across these layers included *CXCL8*, *IL6*, *PTGS2*, *MMP9*, *VEGFA*, *FLT1*, *LCN2*, *DUSP1*, *PPARG*, *PPARGC1A*, and *SOD2*. Cell-cycle regulators (*CCNB1*, *CCNB2*, *CDK1*, *MKI67*, *BIRC5*, and *AURKA*) were linked to DB terms associated with cell activation and movement, and ML pathways related to proliferation and tissue remodeling. Together, the phytochemical target space is positioned to modulate dominant chemokine-cytokine-matrix-angiogenic circuitry and immunometabolic stress programs characteristic of psoriasis.

2.8 Network interaction analysis of psoriasis-associated targets through PPI

To examine the interaction patterns among psoriasis-associated molecular targets, five DEGs (*CCNB1, CDK1, MMP9, PTGS2, CYP1A1*) and the upstream regulator *CREB1*, together with their downstream transcriptional targets. The targets were examined in STRING (v12.0), and the network was then imported into Cytoscape for visualization and topology analysis. The PPI network displayed a highly interconnected topology characteristic of inflammation-associated regulatory systems (Figure 5). (Refer to Section 3.9). Maximal Clique Centrality (MCC) was used to rank

the hub nodes using the algorithm in cytoHubba. *JUN*, *FOS*, *CREB1*, *IL6*, *CXCL8*, *PPARG*, *MMP9*, and *PTGS2* emerged as top-ranked hubs, indicating central roles in transcriptional regulation, cytokine signaling, and metabolic control. Two dominant regulatory modules were evident: an *AP-1* complex formed by the (*FOS/JUN*) dimer, and a *CREB1* driven transcriptional circuit. These modules connect immune signaling with metabolic and stress-responsive transcriptional programs, supporting *CREB1* as a key upstream integrator in psoriatic lesions.

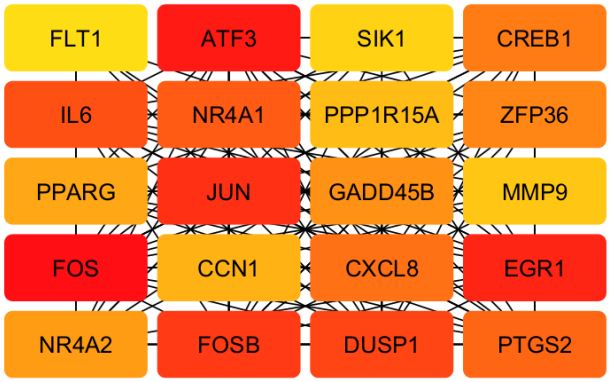

Fig. 5 Protein-protein interaction network of psoriasis-related targets and CREB1-associated genes. Node color reflects centrality, with red nodes marking major hubs.

2.9 Functional enrichment of PPI network using STRING

Functional enrichment analysis of the STRING-derived protein-protein interaction network showed significant over-representation of immune and transcription-related pathways in both Reactome and Gene Ontology (GO) categories. Reactome enrichment highlighted major inflammatory and stress-response signaling cascades, including Cytokine Signaling in the Immune System, MAPK Signaling, NF-κB Activation, IL-17 Signaling, TNF Signaling, and Transcriptional Regulation by CREB1. These pathways reflect cytokine-mediated inflammation, MAPK/NF-κB-associated stress signaling, and CREB1-linked transcriptional regulation in psoriatic lesions. GO Biological Process enrichment highlighted cytokine response, inflammatory signaling, RNA polymerase II-dependent transcriptional activation, and epithelial cell proliferation. GO Cellular Component analysis indicated predominant localization in nucleoplasm, cytosol, transcription factor complexes, and plasma membrane, consistent with transcriptional and signaling-associated proteins. GO Molecular Function categories included DNA-binding transcription factor activity, serine/threonine kinase activity, & cytokine receptor binding, consistent with coordinated transcriptional and signaling regulation. The complete enrichment results are in **Supplementary File 2**.

2.10 Tripartite network linking phytochemicals, gene targets, and pathways

To integrate molecular insights from PPI and enrichment analysis with phytochemical interventions, a tripartite network was constructed linking phytochemicals with new disease associations, their gene targets, and psoriasis-associated pathways (Figure 6). Gene targets of each phytochemical were queried in the CTD database to retrieve associated pathways, which were then intersected with psoriasis-relevant pathways derived from enrichment analyses. The intersecting pathways were retained as biologically meaningful convergence points where phytochemical targets map onto disease-relevant signaling modules. The complete dataset is provided in **Supplementary File 10**. ((Refer to Section 3.10)) The resulting network captures multi-layered interactions across three biological tiers: (i) phytochemicals with new disease associations (mahanine, atractylon, protopine, annomontine, taraxasterol, tricin, and tamarixetin); (ii) their 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* influences *CREB1*, and is associated with metabolic and inflammatory signaling pathways, including PI3K-Akt, AMPK, and TNF pathways, supporting roles in metabolic and immune regulation. *Protopine* and *Annomontine* act via *CYP1A1*, and are linked to metabolic and xenobiotic processing pathways, such as retinol metabolism, tryptophan metabolism, and cytochrome P450-mediated xenobiotic metabolism. *Taraxasterol* targets *MMP9*, engaging IL-17 and TNF Signaling Pathways central to psoriatic inflammation. *Tricin* and *Tamarixetin* converge on *PTGS2*, influencing IL-17, NF-κB, and VEGF associated signaling involved in cytokine-driven inflammation and angiogenesis.

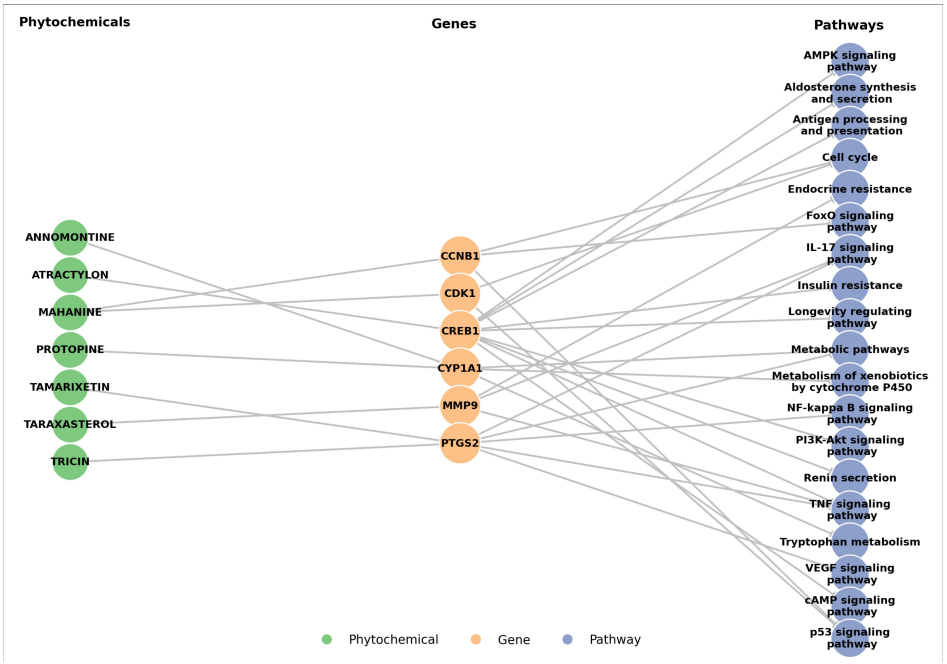

Fig. 6 Tripartite network linking phytochemicals, gene targets, and psoriasis-associated pathways. The network is organized into three biological layers: phytochemicals (green), their validated or predicted gene targets (orange), and psoriasis-related pathways (blue). Edges indicate experimentally supported or literature-derived relationships.

3 Methods

This study applied a transcriptomic-systems biology workflow to identify and prioritize phytochemicals that may modulate psoriasis biology. Figure 7 summarizes the overall analytical workflow used in this study.

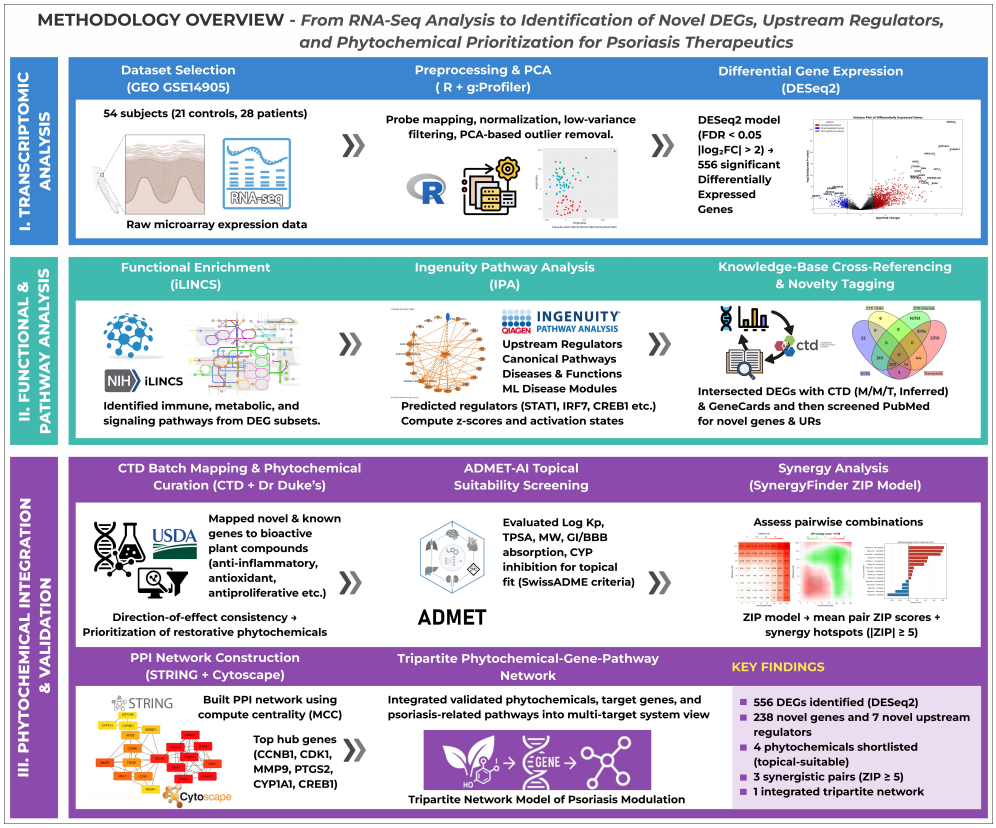

Fig. 7 Overall methodology workflow illustrating dataset selection, preprocessing, differential expression analysis, knowledge-base cross-referencing with evidence tiering, pathway and regulator analysis (iLINCS, IPA), CTD-based chemical mapping with phytochemical curation, ADMET screening for topical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

3.1 Data Preprocessing and Exploratory Analysis

Gene expression profiles were retrieved from the NCBI GEO repository *GSE14905*, generated using the microarray platform (GPL570) [32]. The dataset comprised 82 samples obtained from 54 individuals, including 21 healthy controls, 28 psoriasis patients with paired lesional and non-lesional biopsies (56 samples), and 5 additional lesional-only samples. Probe IDs were converted to gene symbols using the HG-U133Plus2.db annotation via the g:profiler platform [33]. For quality assessment, genes with minimal expression variance were filtered out. Then Principal component analysis (PCA) was applied to the gene-level expression matrix to evaluate sample clustering and detect outliers (Figure 1A). Three lesional samples were identified as outliers and removed before subsequent analyses [34]. The final dataset used for downstream analysis consisted of 21 healthy control samples and 30 lesional samples.

3.2 Differential Gene Expression Analysis

Differential gene expression analysis was performed using the limma package in R [35]. Genes were considered significantly altered if they satisfied the following criteria: p-value less than 0.05, adjusted p-value (FDR) less than 0.05, and absolute $\log_2$ fold change greater than 2 or less than -2 [36]. A volcano plot was generated from the resulting statistics to visualize DEG distribution.

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

To interpret the biological relevance of the identified DEGs, gene lists were systematically compared with psoriasis-associated entries in the Comparative Toxicogenomics Database (CTD) and GeneCards [29, 30]. 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* [31]. To guide downstream prioritization, two tiers were defined *a priori* (i) new-association candidates, operationally defined as DEGs absent from CTD (inferred) and GeneCards and 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 enrichment analysis was conducted through the iLINCS platform [37, 38] using three predefined DEG gene sets: (1) DEGs $\cap$ CTD inferred; (2) DEGs $\cap$ CTD inferred $\cap$ GeneCards; (3) DEGs $\cap$ CTD MM/T $\cap$ GeneCards. Enrichment outputs (terms, statistics, and gene memberships) were retained for functional interpretation.

3.5 Ingenuity Pathway Analysis (IPA)

The DEG matrix containing $\log_2$ fold-change and adjusted p-values was imported into Ingenuity Pathway Analysis (IPA, QIAGEN) for downstream regulatory and pathway modeling. Analyses included Upstream Regulators (UR), Canonical Pathways (CP), Diseases & Biofunctions (DB), and ML Disease Pathways (MLD) [39]. IPA leverages a large, curated knowledge base of molecular interactions and experimental findings, enabling context-specific predictions of pathway activity and regulator impact. This facilitated mapping of transcriptomic signatures onto biological mechanisms and putative therapeutic targets. Table 2 outlines the analysis types and applied filters. 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 screening flagged regulators with potential new gene-disease associations.

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 and high-evidence genes). Retrieved chemicals were filtered against the Dr. Duke's Phytochemical and Ethnobotanical Database to retain compounds with psoriasis-relevant bioactivities (antimicrobial, anti-inflammatory, antiproliferative, antioxidant, anti-angiogenic, antipruritic) [40]. 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 activation of downregulated targets. Downstream analyses focused on two tiers: (i) phytochemicals interacting with new-association candidate genes, 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 as new-association candidates..
2. Map IPA Canonical Pathways, Diseases & Biofunctions, and ML Disease Pathways to tiered genes and their associated phytochemicals.
3. Construct regulatory networks among tiered genes, phytochemicals, and enriched 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* [41] 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 [42] (Table 3), prioritizing low BBB permeability, acceptable skin permeability/retention, and minimal CYP liabilities. Filter thresholds were flexibly adjusted for high-value leads intended for low-percentage (< 1-2%) dermal use and advanced carriers (e.g., nanoemulsions)[43].

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 [44]
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.

3.8 In Silico Synergy Analysis

Pairwise pharmacodynamic effects among shortlisted phytochemicals were analyzed using SynergyFinder tool with the zero interaction potency (ZIP) reference model [45]. Dose-response matrices were created for each compound pair over predetermined concentrations ranges (nM), and normalized as relative inhibition. Deviations from the theoretical non-interaction surface were quantified as ZIP synergy scores, where positive values indicate synergy and negative values indicate antagonism. ZIP scores were computed for each concentration pair to generate two-dimensional synergy landscapes and aggregated into mean pairwise ZIP scores for comparison. Regions with $|\text{ZIP}| \geq 5$ were defined as synergy hotspots and used to prioritize cooperative or antagonistic interactions.

3.9 Protein-Protein Interaction Network Analysis and Functional Enrichment

Interaction data among selected gene targets and upstream regulators were obtained from the STRING database (v12.0) using a high-confidence threshold (score greater than 0.7) [46]. The interaction network was then visualized and analyzed in Cytoscape v3.9.1 [47]. Node centrality was quantified using cytoHubba [48] with Maximal Clique Centrality (MCC) algorithm. Functional enrichment (Reactome and GO BP/CC/MF) was performed through STRING using FDR-adjusted $p < 0.05$.

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 Construction of a Phytochemical-Gene-Pathway Tripartite Network

Shortlisted phytochemicals, their gene targets, and psoriasis-related pathways were assembled into a tripartite network representing multi-layer interactions. Overlapping pathways were retained to reflect disease-relevant intersections. We defined genes by the set G and compounds by the set C. 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 a multi-system inflammatory disorder in which cytokine signaling intersects with antiviral responses and metabolic stress pathways rather than operating as an isolated skin disease [49]. In this study, transcriptomic and network analyses of GSE14905 reproduced this integrated architecture at the gene level. Lesional samples showed coordinated activation of interferon-related modules alongside classical IL-17/TNF inflammatory circuits, consistent with systems-level models of psoriasis [50]. At the pathway level, enrichment analysis recovered IL-17, TNF, and Toll-like receptor signaling, which are established drivers of keratinocyte activation and leukocyte recruitment [51]. In parallel, strong activation of the interferon α/β pathways and nucleic-acid-sensing modules sustained antiviral-like signaling within lesional tissue. Similar interferon signatures have been documented in psoriatic plaques and

are associated with increased antimicrobial peptides and interferon-stimulated gene expression [52, 53]. Together, these results support the interpretation that psoriatic inflammation reflects overlapping immune circuits rather than a single dominant axis [54]. Consistent with this broader immune-stress framework, ML pathway results highlighted oxidative stress and metabolic traits linked to systemic comorbidity patterns. These signals align with evidence connecting chronic inflammatory signaling in psoriasis to oxidative imbalance and cellular senescence-associated mechanisms beyond the skin [55]. Overall, our results reinforce an immunometabolic view in which interferon programs intersect IL-17/TNF signaling and metabolic/vascular risk features [56]. Network-based reduction further condensed hundreds of DEGs into a compact, hub-centered architecture using STRING-Cytoscape. This structure connected inflammatory, angiogenic, and metabolic pathways into a dense regulatory core, suggesting that lesion biology is organized around a limited number of high-connectivity nodes. Similar hub-dominated organization has been reported across chronic inflammatory diseases and is associated with persistent pathway activation [57]. Within the inferred network, AP-1 complexes and CREB1 emerged as dominant transcriptional integrators. This observation is supported by the PPI hub ranking, which placed JUN, FOS, and CREB1 among the most central nodes, and by the CREB1 downstream target set spanning cytokine, metabolic, and proliferation-associated genes. Experimental work supports a mechanistic role for AP-1 in psoriasis-related immune signaling, including IL-23/chemokine programs and keratinocyte activation and differentiation [58]. CREB1 is similarly positioned to connect stress-response and survival programs with inflammatory signaling [59]. Functional enrichment of the PPI network further placed these hubs at the intersection of cytokine signaling, MAPK/NF-κB pathways, and metabolic control, linking inflammatory stimuli to proliferation, oxidative stress responses, angiogenesis, and lipid homeostasis [60]. Consistent with this integrated structure, matrix-angiogenic and metabolic mediators also appeared as central nodes. MMP9 and VEGFA/FLT1 contribute to dermal remodeling and neovascularization in psoriatic tissue [61], while PPARG and PTGS2 connect lipid/eicosanoid metabolism with cytokine amplification and keratinocyte behavior [62]. The concentration of signaling flow through a limited set of transcriptional hubs is consistent with systems models in which chronic inflammation is stabilized by reinforced regulatory circuits rather than transient pathway engagement [57]. Notably, several genes that we classified as having new disease associations clustered into functional categories linked to inflammation and cell migration, suggesting that parts of the psoriasis network remain incompletely characterized at the gene level despite well-established biological processes such as immune cell infiltration and epidermal migration [63]. Building on this systems-level structure, we mapped phytochemicals onto the inferred psoriasis network to generate candidate intervention hypotheses. The shortlisted compounds - mahanine, taraxasterol, tricin, tamarixetin, annomontine, protopine, and atractylon - did not converge on a single molecular target. Instead, they intersected multiple regulatory nodes, which may be advantageous in a disease maintained by interacting cytokine, remodeling, and metabolic circuits rather than a single driver pathway. Mechanistically, the prioritized compounds mapped to complementary functional layers captured in the tripartite network. Mahanine targeted CCNB1 and CDK1 and

mapped to cell-cycle pathways, consistent with modulation of keratinocyte hyperproliferation. Taraxasterol targeted MMP9 and intersected IL-17/TNF signaling, linking it to tissue remodeling and inflammatory amplification. Tricin and tamarixetin converged on PTGS2 and mapped to inflammatory and angiogenic modules through NF-κB and VEGF-related pathways [REF]. Atractylon mapped to CREB1 and to PI3K-Akt/AMPK-associated modules, while protopine and annomontine mapped to CYP1A1 and xenobiotic/retinoid metabolism pathways, suggesting potential roles in detoxification-linked regulatory balance. These assignments are derived from network and database integration and should be interpreted as mechanistic hypotheses rather than direct biochemical evidence. Topical suitability differed substantially across the compound set, consistent with ADMET-AI predictions reported in the Results. Protopine and atractylon displayed physicochemical profiles compatible with passive dermal penetration, whereas more polar flavonoids (e.g., tricin and tamarixetin with high TPSA) and highly lipophilic triterpenes (e.g., taraxasterol with very high LogP) showed limited predicted passive diffusion. Reduced permeability does not negate biological relevance, but it implies the need for formulation strategies such as nano-carriers or penetration enhancers, or consideration of adjunct/systemic roles [64]. Synergy modeling further supported a combination-based strategy while emphasizing the need for empirical optimization. Several compound pairs showed positive ZIP synergy at specific, often asymmetric dose ratios, suggesting that pathway-active compounds with limited permeability may still contribute functional benefit when paired with complementary partners. At the same time, antagonistic interactions - particularly in atractylon-associated pairs - indicate that multi-compound formulations cannot be assumed to be beneficial and must be experimentally refined. Finally, we emphasize that the present study integrates CTD/IPA/STRING mapping, ADMET prediction, and synergy modeling to generate a prioritized, testable hypothesis space rather than establish causal mechanisms. The shortlisted phytochemicals and combinations therefore define a focused validation agenda. Immediate next steps include testing hub modulation and compound pairing in keratinocyte-immune co-culture systems and organotypic skin models, followed by formulation development for topical delivery and assessment of efficacy and safety in psoriasis-relevant experimental settings.

5 Conclusion

This study shows that psoriasis is driven by an interferon-centred, immunometabolic and transcriptional coordinated network rather than a purely cytokine-driven process. Lesional skin displayed strong IL-17/TNF/TLR and HIF-1 signaling alongside metabolic rewiring and a dominant type I/III interferon signature regulated by *STAT1*, *IRF1*, *IRF3* and *IRF7*. Network and functional enrichment analyses positioned *AP-1* (FOS/JUN) and *CREB1* as central regulatory hubs linking inflammatory, metabolic, and matrix-remodeling pathways through key effectors such as *IL6*, *CXCL8*, *MMP9*, *FLT1*, *PPARG* and *PTGS2*. Phytochemical mapping identified seven natural compounds capable of targeting these disease-associated nodes. ADMET profiling highlighted protopine and atractylon as the most suitable candidates for

topical delivery, while mahanine emerged as a potent but formulation-dependent scaffold. Tricin, tamarixetin and taraxasterol showed limited standalone topical suitability but contributed important mechanistic and synergy insights. Synergy analysis further identified cooperative interactions among flavonoid-alkaloid pairs, including protopine-annomontine, annomontine-tamarixetin, and tricin-mahanine, suggesting that rational multi-target combinations may achieve greater biological activity than single agents. Overall, this multi-layered framework provides a mechanism-driven shortlist of phytochemicals and combinations targeting the IL-17/TNF-interferon-AP-1/CREB1-COX-2/MMP9 axis in psoriasis. Experimental validation in keratinocyte and organotypic skin models will be necessary to determine whether these compounds, alone or in combination, can effectively rebalance psoriatic signaling in vivo.

5.1 Data and Code Availability

GitHub repository contains all analysis scripts, processed datasets, and supplementary files generated in this research work: https://github.com/rishemjit/Psoriasis. The repository includes the following analysis files:

- **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.
- **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 Analysis

Gene Ontology (GO) enrichment was analyzed independently for the three DEG subsets (556, 179, and 43 genes). The complete enrichment outputs for each subset are available in Supplementary File 2. To reduce false positives, we applied a stringent cutoff requiring both raw $p < 0.05$ and adjusted $p < 0.05$. Under this threshold, the 179 DEG subset did not show statistically significant GO biological process enrichment. In contrast, the 556 DEG subset was used to construct an enrichment map in Cytoscape, allowing visualization of functional relationships as a network. Using normalized enrichment scores (NES), three dominant GO biological process modules were observed (Figure A1A):

- Regulation of metabolic and transcriptional processes (65 GO terms)
- Defense/immune/viral response (6 GO terms)
- Chromosome segregation and nuclear division (4 GO terms)

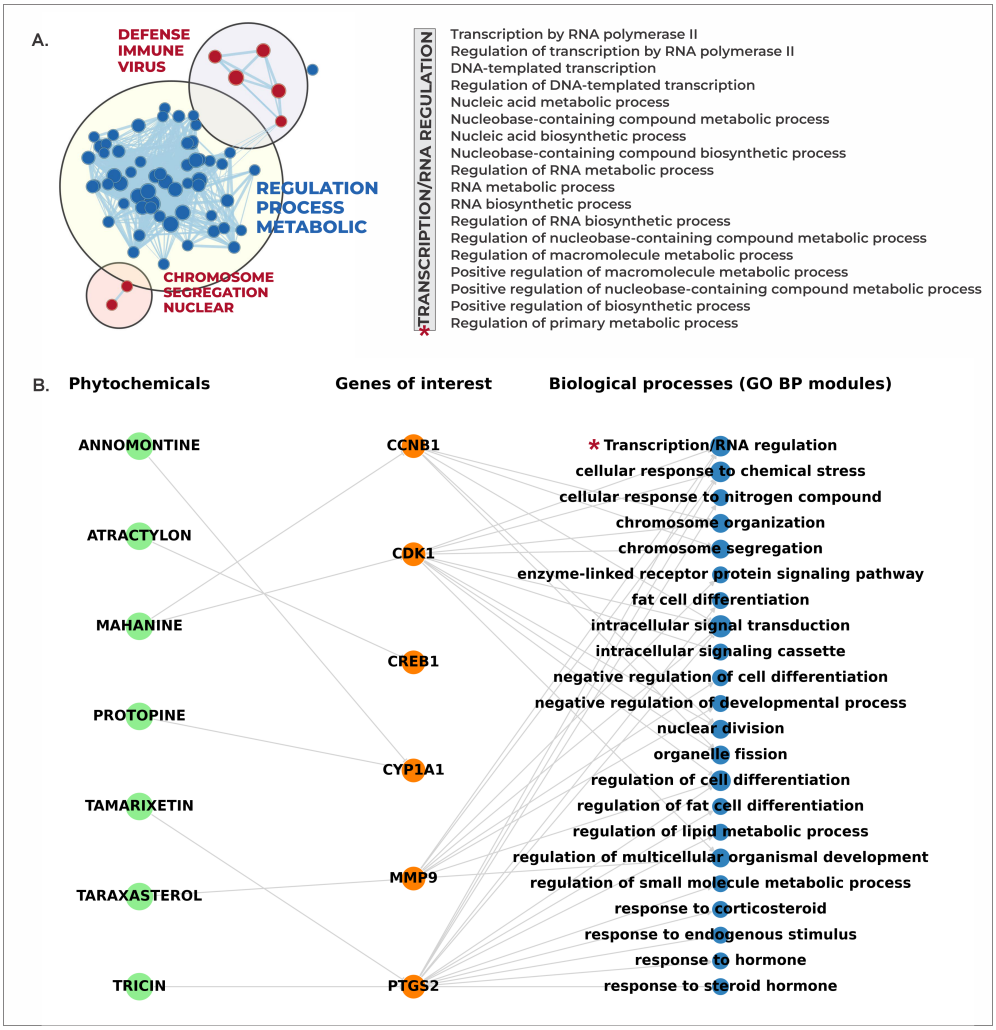

Fig. A1 (A) Cytoscape enrichment map of GO biological processes for the 556 DEG subset. Each circle represents a biological process, and connecting lines show shared genes between processes. Red nodes indicate positively enriched terms, while blue nodes indicate negatively enriched terms. Groups of connected nodes form functional modules. (B) Tripartite network connecting phytochemicals, gene targets, and biological processes, showing how multiple compounds influence shared regulatory pathways. The starred transcription/RNA regulation module appears as a central cluster linking metabolic regulation, stress response, and cell differentiation.

During downstream network construction, eight development-related ontologies were removed to keep the focus on processes more directly related to cellular regulation. Within the regulation/metabolic module, several enriched terms were associated with transcriptional control, nucleic acid metabolism, and hormone-responsive

regulatory pathways. Some of these biological themes are less emphasized in psoriasis-focused literature, including epithelial morphogenesis, nucleobase metabolism, RNA polymerase II-linked transcriptional regulation, steroid hormone response, and broader multicellular developmental regulation. The full list of NES-significant biological processes for the 556 DEG set is provided in Sheet 3 of Supplementary File 2. The remaining modules (29 + 14 ontologies combined) represent processes that are already well documented in psoriasis literature. These were not expanded further in the main text and are included in Sheet 4 of Supplementary File 2 for reference. To examine how the candidate phytochemicals interact with genes within these modules, a tripartite network was built connecting phytochemicals, gene targets, and enriched biological processes (Figure A1B). The network shows that several phytochemicals converge on shared regulatory hubs, particularly genes involved in transcriptional control and cell cycle activity. These genes are connected to broader processes such as intracellular signaling, chromosome organization, and metabolic regulation. The network suggests that these compounds influence groups of related regulatory pathways at the same time. Several phytochemicals affect overlapping sets of genes, pointing to shared functions or combined effects at the system level.

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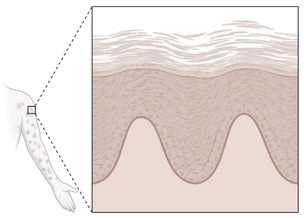
METHODOLOGY OVERVIEW - *From RNA-Seq Analysis to Identification of Novel DEGs, Upstream Regulators, and Phytochemical Prioritization for Psoriasis Therapeutics*

I. TRANSCRIPTOMIC ANALYSIS

Dataset Selection (GEO GSE14905)

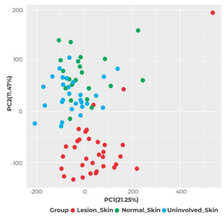
54 subjects (21 controls, 28 patients)



Raw microarray expression data

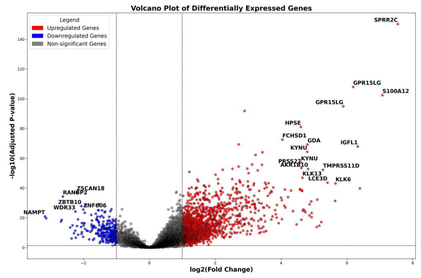
Preprocessing & PCA (R + g:Profiler)

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

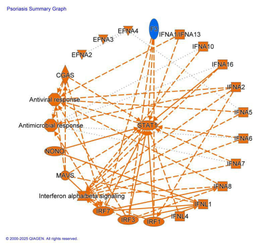


II. FUNCTIONAL & PATHWAY ANALYSIS

Functional Enrichment (iLINCS)

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

Ingenuity Pathway Analysis (IPA)

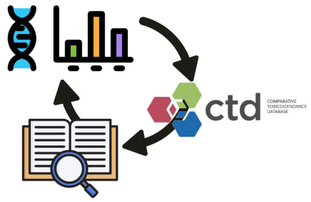


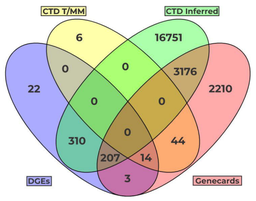
INGENUITY PATHWAY ANALYSIS

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

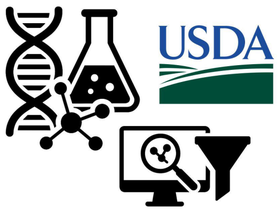




Intersected DEGs with CTD (M/M/T, Inferred) & GeneCards and then screened PubMed for novel genes & URs

III. PHYTOCHEMICAL INTEGRATION & VALIDATION

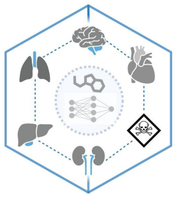
CTD Batch Mapping & Phytochemical Curation (CTD + Dr Duke's)



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

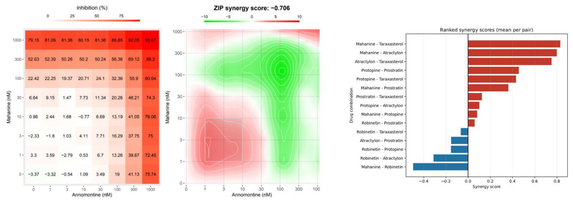


ADMET

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

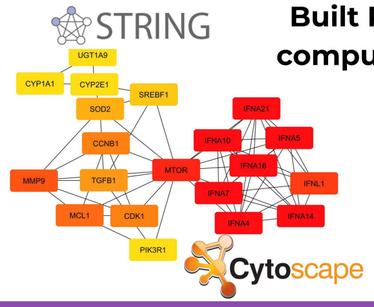
Synergy Analysis (SynergyFinder ZIP Model)

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)

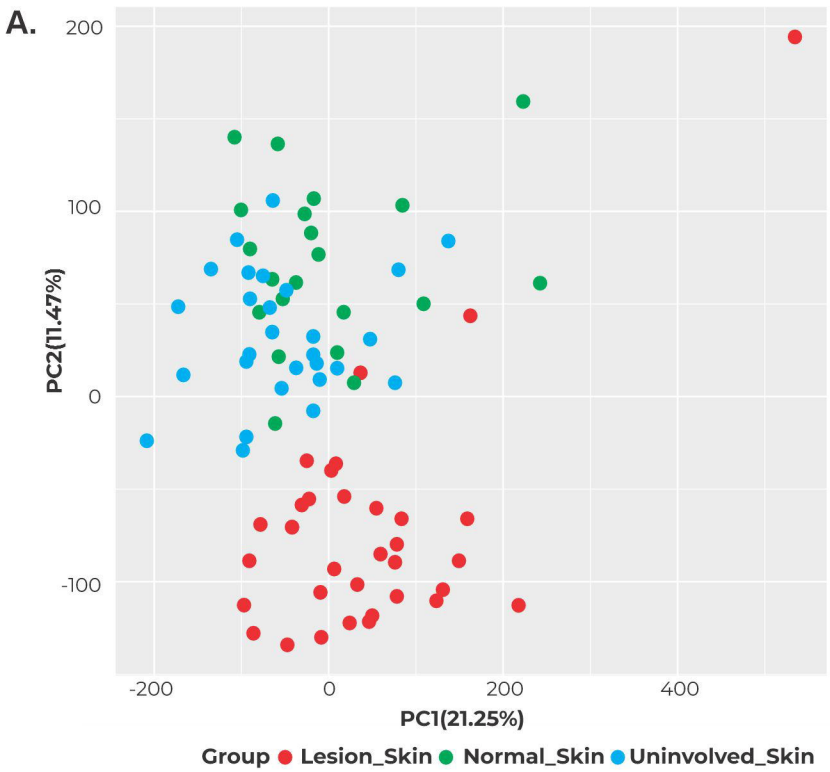
Tripartite Phytochemical-Gene-Pathway Network

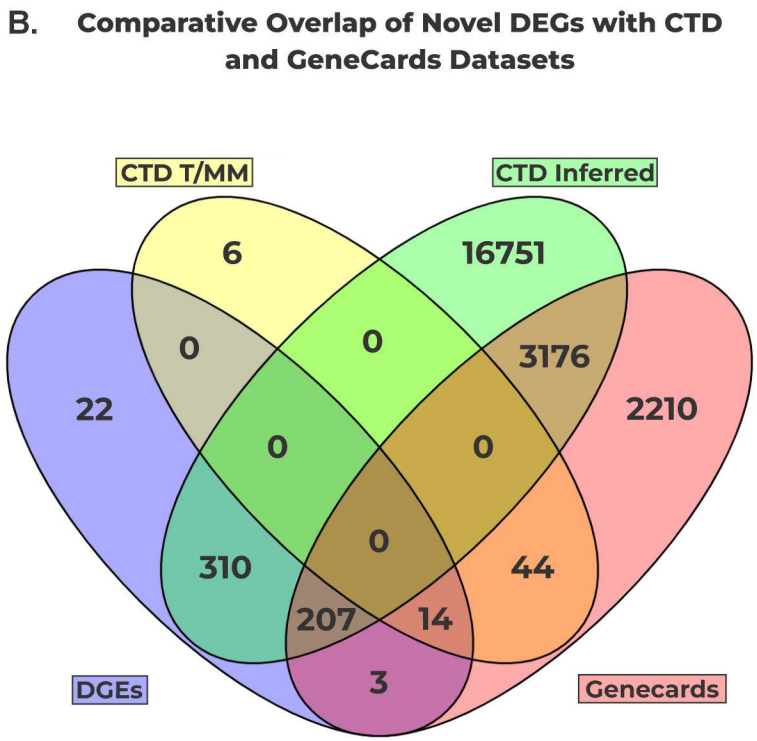
Integrated validated phytochemicals, target genes, and psoriasis-related pathways into multi-target system view

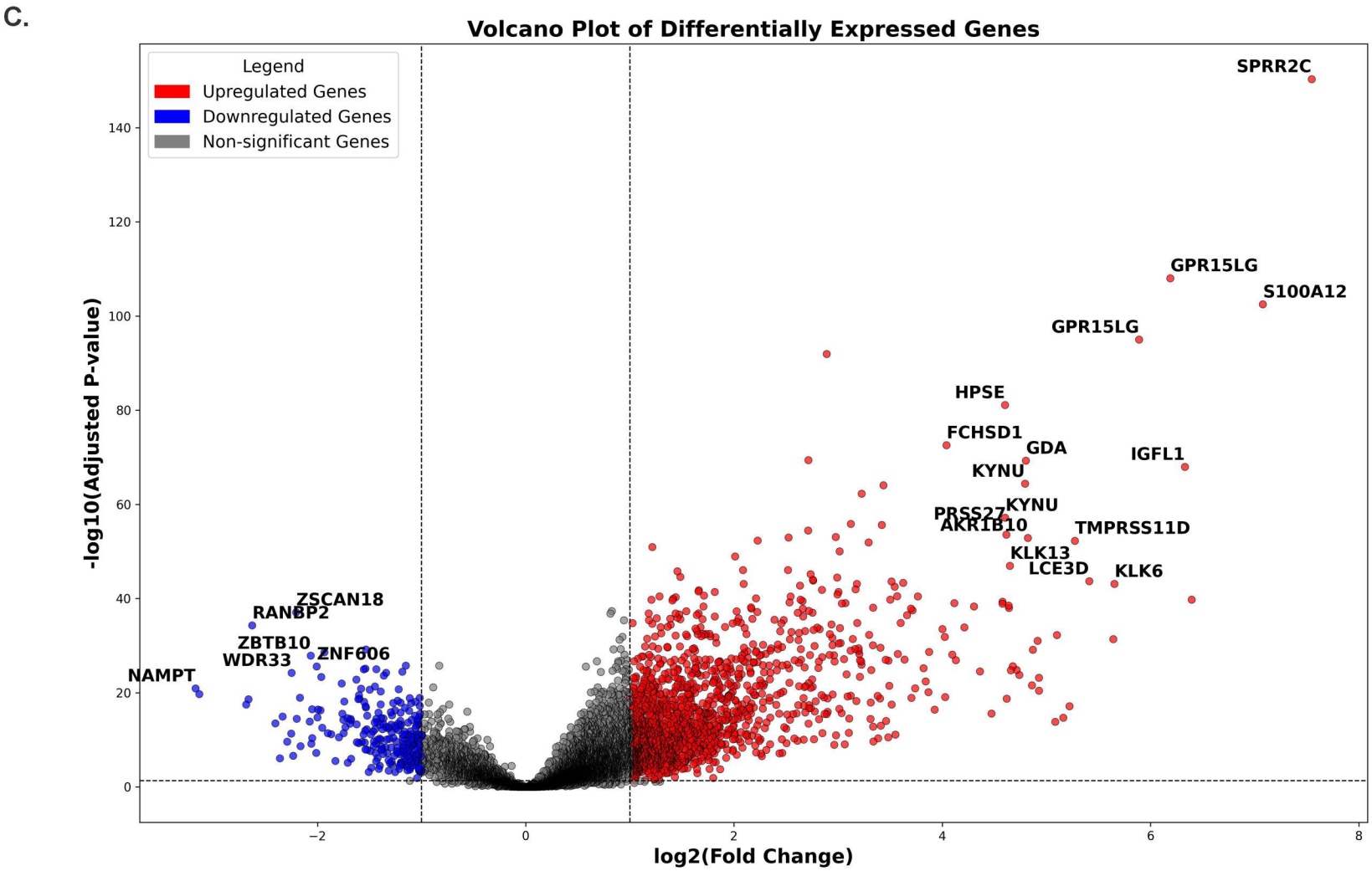
Tripartite Network Model of Psoriasis Modulation

KEY FINDINGS

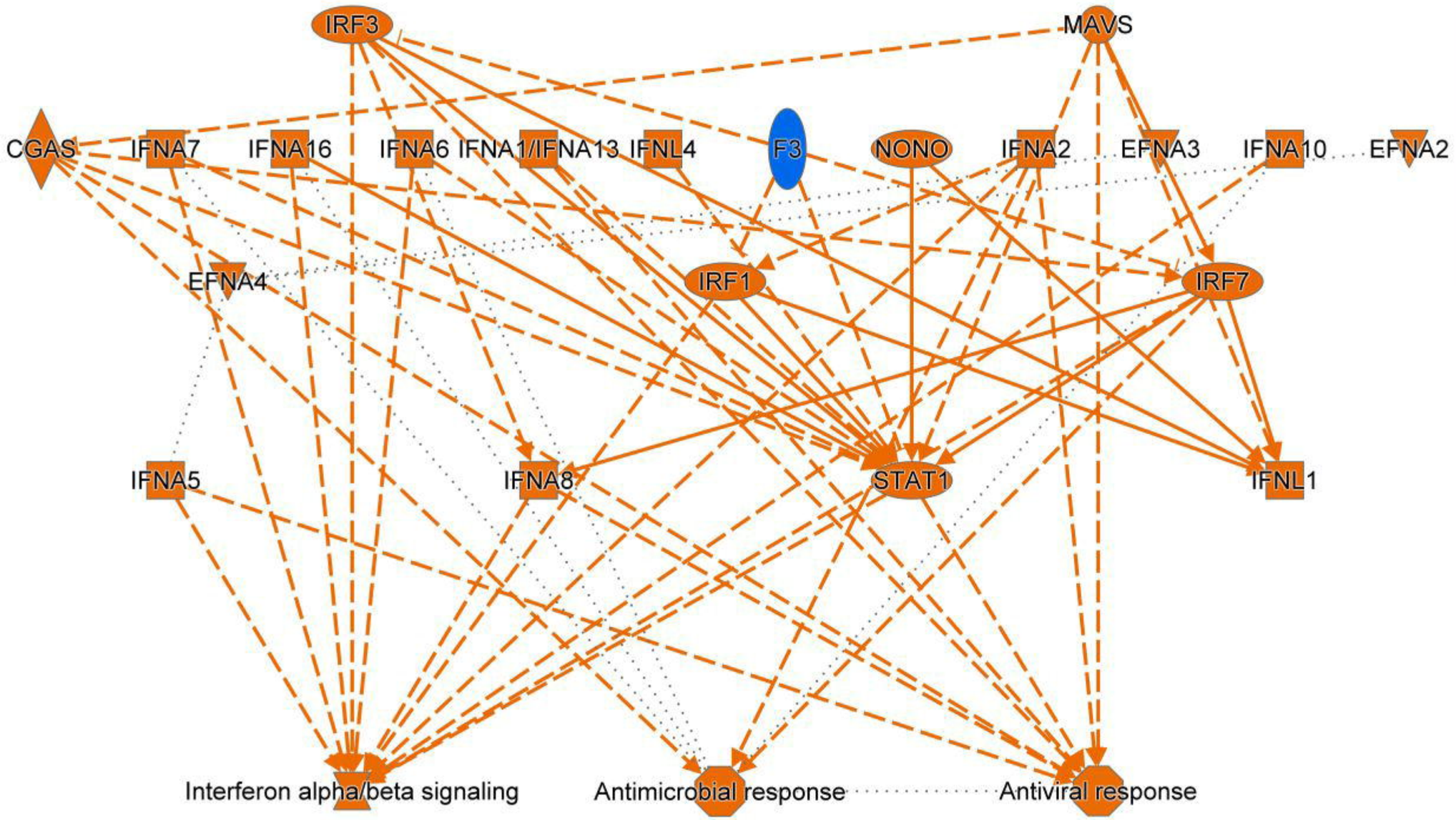
- 556 DEGs identified (DESeq2)
- 238 novel genes and 7 novel upstream regulators
- 4 phytochemicals shortlisted (topical-suitable)
- 3 synergistic pairs (ZIP ≥ 5)
- 1 integrated tripartite network


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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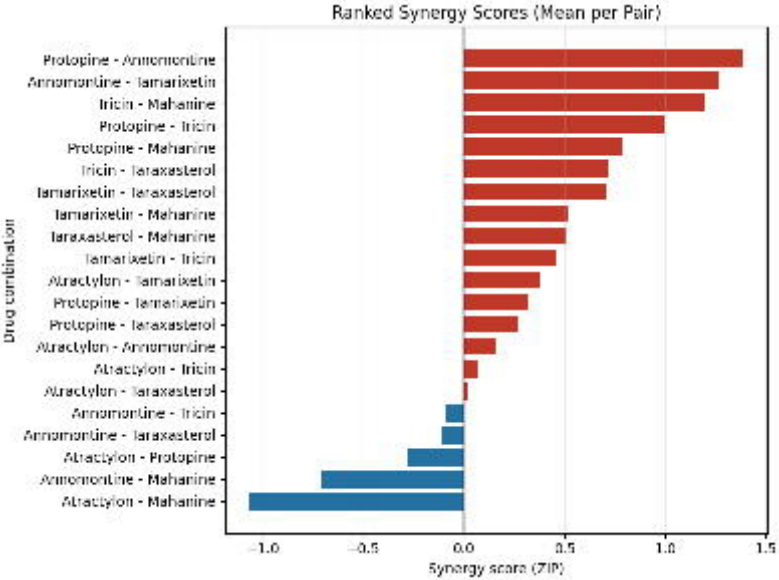
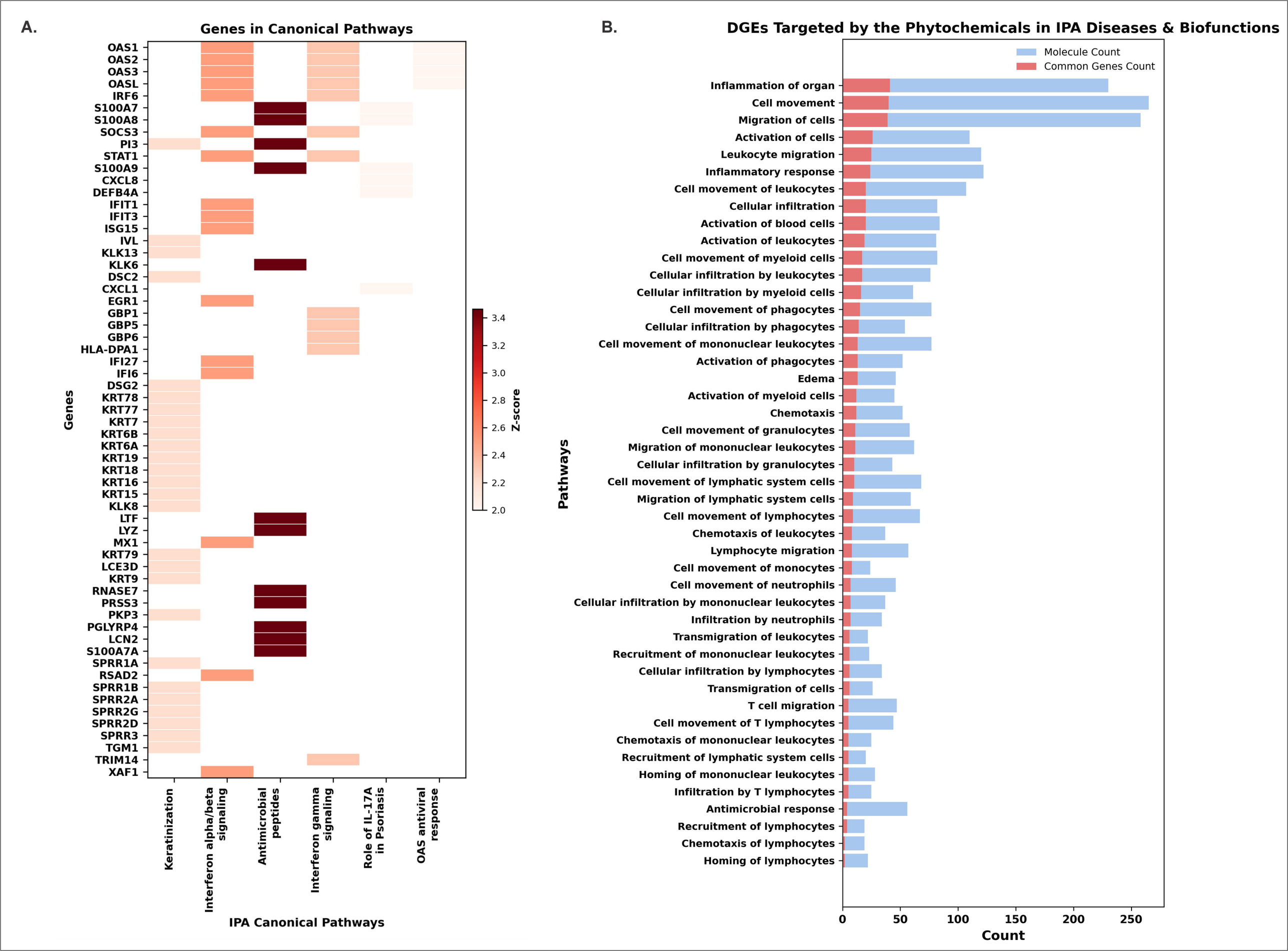
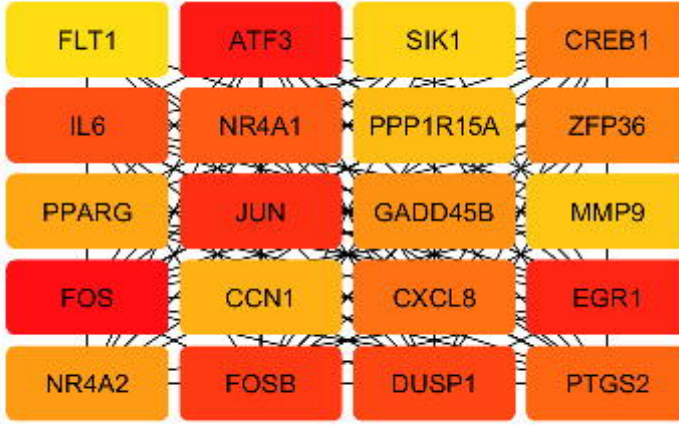
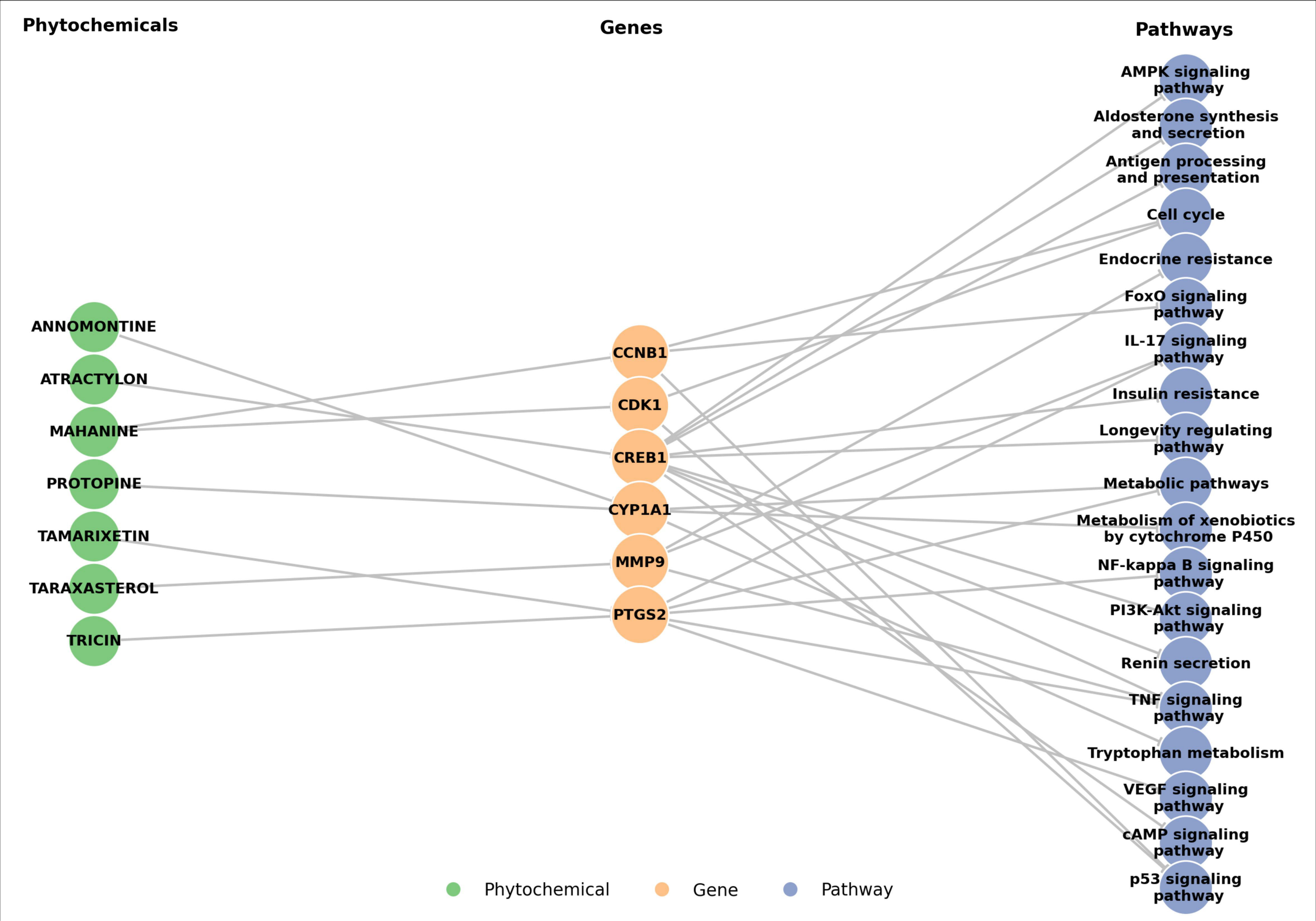
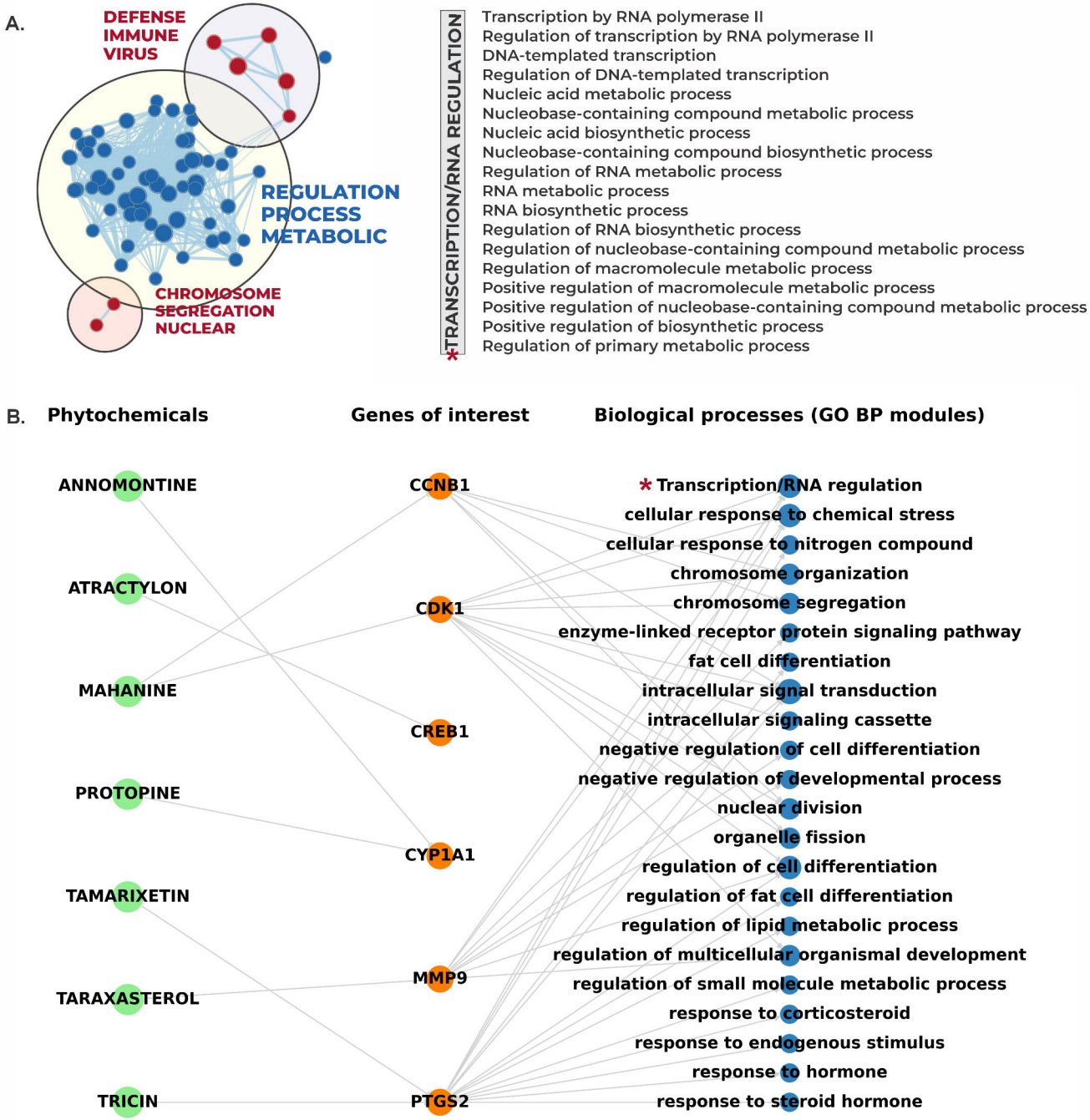

Ranked Synergy Scores (Mean per Pair)
Protopine - Ammorontine
Ammorontine - Tamarixetin
Tricin - Mahanine
Protopine - Tricin
Protopine - Mahanine
Tricin - Taraxasterol
Tamarixetin - Taraxasterol
Tamarixetin - Mahanine
Taraxasterol - Mahanine
Tamarixetin - Tricin
Atractylon - Tamarixetin
Protopine - Tamarixetin
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


A.
DEFENSE
IMMUNE
VIRUS
REGULATION
PROCESS
METABOLIC
CHROMOSOME
SEGREGATION
NUCLEAR
*TRANSCRIPTION/RNA REGULATION
Transcription by RNA polymerase II
Regulation of transcription by RNA polymerase II
DNA-templated transcription
Regulation of DNA-templated transcription
Nucleic acid metabolic process
Nucleobase-containing compound metabolic process
Nucleic acid biosynthetic process
Nucleobase-containing compound biosynthetic process
Regulation of RNA metabolic process
RNA metabolic process
RNA biosynthetic process
Regulation of RNA biosynthetic process
Regulation of nucleobase-containing compound metabolic process
Regulation of macromolecule metabolic process
Positive regulation of macromolecule metabolic process
Positive regulation of nucleobase-containing compound metabolic process
Positive regulation of biosynthetic process
Regulation of primary metabolic process
B.
Phytochemicals
Genes of interest
Biological processes (GO BP modules)
ANNOMONTINE
ATRACTYLON
MAHANINE
PROTOPINE
TAMARIXETIN
TARAXASTEROL
TRICIN
CCNB1
CDK1
CREB1
CYP1A1
MMP9
PTGS2
* Transcription/RNA regulation
cellular response to chemical stress
cellular response to nitrogen compound
chromosome organization
chromosome segregation
enzyme-linked receptor protein signaling pathway
fat cell differentiation
intracellular signal transduction
intracellular signaling cassette
negative regulation of cell differentiation
negative regulation of developmental process
nuclear division
organelle fission
regulation of cell differentiation
regulation of fat cell differentiation
regulation of lipid metabolic process
regulation of multicellular organismal development
regulation of small molecule metabolic process
response to corticosteroid
response to endogenous stimulus
response to hormone
response to steroid hormone