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In Silico Analysis of Tea Leaf Compounds Targeting Inflammatory Pathways and Acne-Related Genes

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Abstract

Acne (*Acne vulgaris*) is a chronic skin disease affected by *Cutibacterium acnes* infection and inflammatory pathways that trigger innate immune responses, such as inflammasome activation. The expression of inflammation-related genes plays a critical role in acne pathogenesis and immune modulation. This study aims to identify compounds from tea leaves (*Camellia sinensis* var. *assamica*) that can treat acne by influencing the expression of inflammatory-related genes through in silico analysis. The GSE6475 dataset was utilized to identify differentially expressed genes (DEGs) between acne-affected and normal skin samples (each group n=6). A total of 573 DEGs were identified and mapped to the KEGG inflammatory pathway. The hub gene analysis results showed six genes, including CXCL1, STAT1, and PIK3 (adj. *P*-value < 0.05). These key genes were then used to cross-validate skin grouping with acne lesions and normal skin. The structure of compounds (natural products) in tea leaves (*C. sinensis* var. *assamica*) was obtained from the PubChem database, and their activity against target proteins associated with the identified key genes was predicted using the SkelSpheres descriptor and Support Vector Regression method. This quantitative structure–activity relationship (QSAR)-based machine learning approach was selected because it enables high-throughput prediction of inhibitory potential using chemical descriptors and experimentally derived bioactivity data, providing broader predictive power than conventional molecular docking or molecular dynamics, which rely mainly on structural and energetic estimations. The in-silico prediction results showed that compounds such as theobromine, assamsaponin, procyanidin, and caffeine have exhibited good predicted activity (IC_{50} ranging from 1.125 to 1.320 μM) as potential inhibitors of the PI3K/Akt pathway, which is known to play a role in the pathogenesis of acne.

Keywords: *Acne vulgaris*, *Camellia sinensis*, differentially expressed genes, key genes, PI3K/Akt

1. INTRODUCTION

Acne vulgaris is a chronic inflammatory skin disorder affecting the pilosebaceous units and affects 9.4% of the global population [1]. Acne presents in various forms, with acne vulgaris accounting for approximately 99% of all cases [1]. Clinically, acne lesions are categorized as non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, nodules, and cysts) [2]. The relationship between acne and the KEGG inflammatory pathway is primarily mediated through activating the immune response triggered by *Cutibacterium acnes* (formerly *Propionibacterium acnes*) and other inflammatory factors. C. acnes infection is a major cause of acne, primarily through its interaction with the Th17 inflammatory pathway, which is activated during lesion formation [3]. In addition, activation of Toll-like receptors (TLRs) and release of proinflammatory cytokines such as IL-1β due to C. acnes infection induce an innate immune response, including

inflammasome activation, further enhancing inflammation [4,5].

Inflammation-related gene expression is critical in acne pathogenesis, highlighting the complex interplay between immune response and skin homeostasis. Key genes include pro-inflammatory cytokines, matrix metalloproteinases, and various receptors that regulate immune cell activity. A study identified 303 differentially expressed genes (DEGs) associated with inflammation, including FPR2, CXCL8, and ICAM1, which are involved in immune system signaling pathways [6]. Genes such as IL-8 and serum amyloid A (SAA1/2) increase expression in acne, while activation of TLR1/2 and TLR4 in sebocytes is known to enhance the inflammatory response during acne pathogenesis [7]. Matrix metalloproteinases (MMP-1 and MMP-3) are significantly upregulated in acne lesions and contribute to inflammation and tissue remodeling [8].

Polyphenolic compounds such as epigallocatechin gallate (EGCG) help reduce inflammation and inhibit the growth of acne-causing bacteria. EGCG has shown strong antibacterial effects against C. acnes while suppressing the expression of pro-inflammatory cytokines such as IL-1, IL-6, and IL-8 in sebocytes, thereby reducing inflammation associated with acne [9,10]. Green tea extract was also found to dose-dependently decrease IL-6 expression in keloid fibroblasts, indicating its efficacy in reducing inflammation and promoting apoptosis [11]. It is known that EGCG is found in various types of tea (*Camellia sinensis*). In Indonesia, the most widely planted type of tea is *assamica* because of its higher productivity. The highest levels are found in younger tea leaves, with significant variation across different tea varieties [12]. The use of an in silico approach has also been carried out by Rachmania et al. [13], who reported that alkaloid compounds from white crinum herb (*Crinum asiaticum*) are predicted to have potential as anti-inflammatory agents.

Based on the explanation above, this study aims to identify compounds in tea leaves (*C. sinensis* var. *assamica*) that may alleviate acne by targeting inflammation-related gene expression in silico. Previous research mainly focused on the antibacterial and antioxidant activities of *C. sinensis*, whereas its potential to modulate inflammatory gene expression in acne remains unclear. To address this gap, we integrated transcriptomic data analysis (GSE6475) from the Gene Expression Omnibus (GEO) database with in silico compound–target prediction to identify potential anti-inflammatory molecules. The dataset used was GSE6475, which contains mRNA microarray data from skin biopsies obtained from inflammatory papules and normal skin of patients with acne, and normal skin biopsies from subjects without acne [8]. The in silico approach was chosen for its efficiency in linking gene expression profiles with predicted bioactivity using the SkelSpheres descriptor–Support Vector Regression (SVR) model, which provides higher predictive accuracy and throughput.

2. RESEARCH METHODS

Instruments and Materials

The in silico analysis was performed using a computer with the following specifications: Windows 11 Pro, Intel Core i7-8665U (1.90 GHz - 2.11 GHz), with 16.0 GB RAM. The analytical tools used in this study were grouped according to their functions. Hub gene analysis, as well as cross-validation process with Principal Component Analysis (PCA) and machine learning, were performed using Orange v3.37.0 [14]. Prediction of compound activity in *C. sinensis* was performed using DataWarrior v6.1.0 [15]. The dataset used for DEGs analysis was GSE6475, which was obtained from the Gene Expression Omnibus (GEO) database. Data on active and inactive compounds against DEG-related proteins were obtained from the ChEMBL database. Data on compounds (natural products) from tea leaves (*C. sinensis* var. *assamica*) were obtained from the PubChem database [16].

Procedures

The first stage of the study was to identify DEGs from the GSE6475 dataset, which contained mRNA microarray expression profile data from inflammatory papule skin biopsies and normal skin [8]. Next, key gene (hub-gene) analysis or genes that overlap from inflammation-related signaling pathways was carried out, and cross-validation of these key genes was subsequently conducted. The second stage was identifying target proteins related to DEGs whose activity would be affected. Furthermore, the compounds in tea leaves (*C. sinensis* var. *assamica*) were predicted for their activity against the target protein (IC_{50} or EC_{50}) using molecular descriptors and machine learning methods.

Identification of DEGs and key genes related to inflammation and their validation

DEGs analysis on the GSE6475 dataset was performed using GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) with P-value correction performed using the Benjamini and Hochberg method with adj. *P*-value < 0.05 [17]. Annotation of DEGs in the Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathway related to inflammation was performed using Enrichr (https://maayanlab.cloud/Enrichr/). From the DEGs mapped to each signaling pathway, the key genes were then determined using Orange v3.37.0. Key genes are genes that have many interactions with other genes [18].

The raw data expression of the key genes generated was then searched in the 'Series Matrix File(s)'. These raw data were then analyzed using Orange v3.37.0 for cross-validation with Principal Component Analysis (PCA) and machine learning.

Activity test of compounds in *C. sinensis* var. *assamica* leaves against target proteins related to key genes

Various active compounds against key gene-related proteins can be obtained from the ChEMBL database through the DataWarrior v6.1.0 application. In DataWarrior, active compound data can be IC_{50} or EC_{50} values tested on key gene-related proteins. Based on the activity value against the protein, a prediction model was made for testing the activity of compounds found in tea leaves (*C. sinensis* var. *assamica*).

The active and inactive compounds against proteins from ChEMBL were grouped into clusters based on structural similarity using the SkelSpheres descriptor. The similarity based on SkelSpheres measures how many circular fragments or atom groups are the same between two molecules, compared to the total number of circular fragments of both molecules [15]. In this study, the similarity level of SkelSpheres was set at 90%. From each group, one representative compound was selected to be used as training data. In contrast, the other compounds were used as testing data to predict their activity using Support Vector Regression (SVR) in DataWarrior. The correlation coefficient (R-square, R^2) value of the graph between actual vs predicted log (IC_{50} or EC_{50}) was calculated, and the model was considered valid if $R^2 > 0.5$ [19]. After the model was considered valid, the prediction of compound activity in tea leaves (*C. sinensis* var. *assamica*) against key gene-related proteins was carried out in the same way as the prediction of activity on the training data. The structure of compounds (natural products) in tea leaves (*C. sinensis* var. *assamica*) was obtained from the PubChem database.

3. RESULTS AND DISCUSSION

The statistical significance and magnitude of changes (fold change, FC) of the DEGs analysis results were visualized with a volcano plot, as shown in **Figure 1**. **Figures 1(a) and (b)** display the differentially expressed genes (DEGs) identified between acne lesions and normal skin, with red dots indicating upregulated genes and blue dots indicating downregulated genes. A total of 573 DEGs were found to distinguish skin with acne lesions from normal skin. In contrast, **Figure 1(c)** shows that no significant DEGs were detected between non-acne skin and normal skin, indicating that their gene expression profiles are highly similar. Furthermore, the UMAP analysis presented in **Figure 1(d)** demonstrates clear clustering of the samples, where non-acne skin is positioned closer to normal skin than to acne lesions. This pattern confirms that the identified DEGs effectively differentiate acne-affected skin from healthy skin. These 573 DEGs were subsequently analyzed using KEGG pathway enrichment (via Enrichr) to explore inflammation-related signaling pathways involved in acne lesion formation.

The results of DEGs mapping on the inflammatory pathway (KEGG) can be seen in Table 1. Nine inflammatory signaling pathways contain 156 DEGs, acne_lesion vs normal_skin or non_acne. Furthermore, DEGs related to the inflammatory pathway were subjected to key gene analysis. Key genes (hub genes) refer to genes that have a key role in the regulation and interaction of gene networks, are usually highly connected to other genes, and significantly influence various biological processes and diseases [20]. The results of the key gene search based on inflammation-related DEGs listed in **Table 1** are shown in **Figure 2** and **Table 2**.

In **Figure 2**, ten differentially expressed genes (DEGs) with the most interactions related to the inflammatory pathway are shown. These DEGs include CCL4, CXCL1, CXCL2, CXCL8, IL1B, MYD88, PIK3R1, PIK3R2, STAT1, and TRAF3. This figure illustrates the interaction network among these genes, highlighting their central roles in inflammation-related signaling. In **Table 2**, these ten DEGs are listed along with their statistical parameters, including Log_2 fold change (Log_2FC) and adjusted p-values ($Padj < 0.05$). This table provides detailed information about the direction and magnitude of expression changes for each gene. From these ten DEGs, those with Log_2FC values greater than |1| were selected and cross-validated based on their expression levels to determine whether they could serve as biomarkers for distinguishing acne lesions from normal skin. Based on this criterion, six DEGs — CCL4, CXCL1, CXCL2, CXCL8, PIK3R2, and STAT1 — were chosen for further cross-validation.

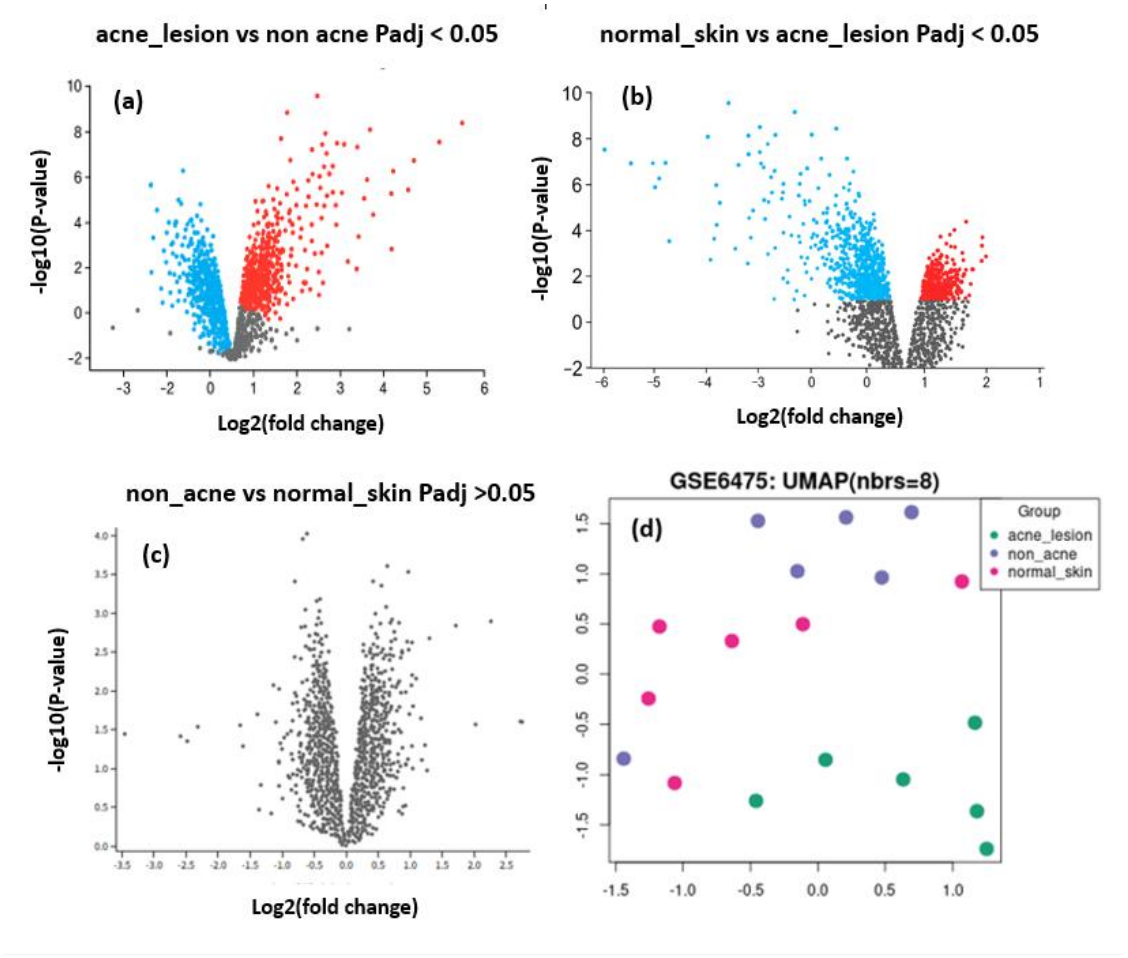

Figure 1. Volcano plot of DEGs analysis results on the GSE6475 dataset.

Table 1. Results of DEGs analysis of the GSE24422 dataset related to inflammatory signaling pathways

Signaling Pathway	Gene
Cytokine-cytokine receptor interaction	IL1RN;TNFRSF6B;CSF3R;CXCL8;EDA;IL20RA;CXCR4;CSF2RB; CXCL1;CXCL13;CXCL2;CXCL5;IL1RL1;CXCR2;CCL4;CCL3; CCL19;CCR5;CCR2;IL12RB2;IL13RA1;CCR1;IL4R;TGFB1;CCL21;IL1R1; IL37;IL36G;IL16;INHBB;OSMR;TNFRSF1B;IL1B
Chemokine signaling pathway	CXCL8;WAS;CXCR4;PIK3R2;CXCL1;PIK3R1;CXCL13;CXCL2; CXCL5;GNG10;CCL4;CXCR2;RAC2;CCL3;CCL19;CCR5;CCR2; CCR1;LYN;CCL21;STAT1;FGR; HCK;PARD3;GRB2
NF-kappa B signaling pathway	LYN;CXCL8;EDA;SYK;BCL2A1;CCL21;IL1R1;CXCL1; CXCL2; ICAM1;PLAU;TRAF3;IL1B;CCL4;CD14;CCL19; MYD88
Toll-like receptor signaling pathway	CD86;CXCL8;STAT1;PIK3R2;PIK3R1;TRAF3;IL1B; CCL4; IRF7; CCL3;SPP1;CD14;MYD88
IL-17 signaling pathway	CXCL8;MMP1;TRAF3;IL1B;MMP3;CXCL1;DEFB4A; CXCL2; S100A9;CXCL5;S100A8;S100A7
TNF signaling pathway	MMP3;PIK3R2;CXCL1;PIK3R1;TNFRSF1B;SELE;CXCL2;CXCL5; ICAM1;TRAF3;IL1B;BCL3;JUNB
NOD-like receptor signaling pathway	CXCL8;STAT1;CYBB;CYBA;CXCL1;CXCL2;IFI16;TRAF3;IL1B; NAMPT;CASP4;IRF7;DEFB4A;MYD88; CTSB
JAK-STAT signaling pathway	CSF3R;IL4R;STAT1;IL20RA;CSF2RB;PIK3R2;PIK3R1;OSMR;PIAS1; GRB2;PTPN2;IL13RA1;MCL1;IL12RB2
MAPK signaling pathway	TGFB1;IL1R1;AREG;PGF;MAPKAPK3;IL1B;KIT;RAC2;GRB2;CD14; MAPT;FGFR2;MYD88;MAP4K4

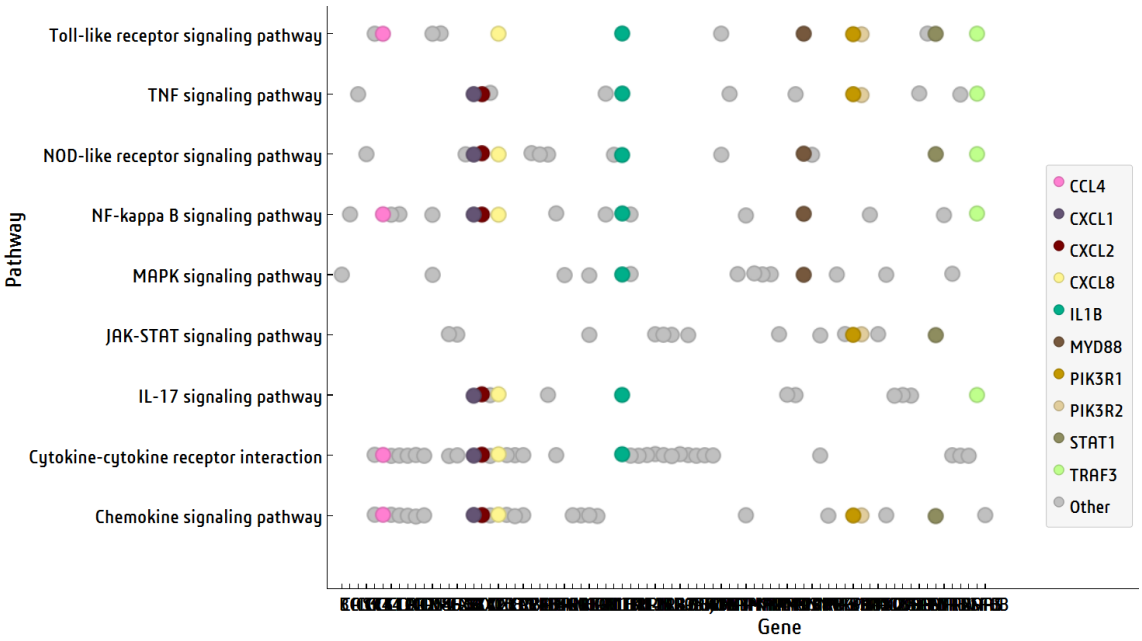

Figure 2. The results for key genes related to inflammatory pathways are derived from the data presented in Table 1

The results of cross-validation using machine learning and PCA are presented in **Figure 3** and **Table 3**. In **Figures 3(a) and 3(b),** no difference were observed between normal skin from patients with acne (normal skin) and without acne (non-acne) based on the 3 DEGs and the 6 DEGs related to inflammation, with the highest ANOVA scores. However, both normal skin types can be significantly distinguished from Acne Lesion based on both 6 DEGs and 3 DEGs. These results are supported by cross-validation using 'support vector machine (SVM), as shown in Table 3. However, it can be seen that 3 DEGs (PIK3R2, CXCL1, and STAT1) are better able to distinguish acne lesions and normal skin compared to using 6 DEGs. SVM is a machine learning algorithm that aims to find a hyperplane that maximizes the margin between different classes and increases classification accuracy [21]. Among them, the SVM model successfully increased the sensitivity and specificity to 100% based on ten-gene biomarkers for diabetes diagnosis [22].

PIK3R2 is part of the PI3-kinase class I (PI3Ks) complex and the PI3Ks/Akt signaling pathway, which regulates cell proliferation and inflammation. Dysregulation of this pathway can lead to increased sebum production and keratinocyte proliferation, both critical in developing acne. In addition, the nuclear transcription factor FOXO1 deficiency may be affected by PIK3R2 signaling and may worsen acne by promoting the expression of acne-related genes [23]. CXCL1 is a chemokine that attracts neutrophils to sites of inflammation. Its upregulation in acne lesions plays a key role in the inflammatory response associated with acne vulgaris. Increased levels of CXCL1 also correlate with acne severity, suggesting its potential as a biomarker for inflammatory activity in acne lesions [24]. STAT1 is involved in the JAK/STAT signaling pathway that mediates immune responses. Its activation in acne lesions suggests a role for STAT1 in the inflammatory process and is potentially related to acne severity [25].

Based on **Table 2**, the Log2FC of CXCL1, STAT1, and PIK3R2 genes is positive or shows overexpression in acne lesions compared to normal skin. Thus, if there is no post-transcriptional modification, the proteins of the three genes also experience the same expression (overexpression). Thus, compounds from tea leaves (*C. sinensis* var. *assamica*) will be predicted to have activity in inhibiting CXCL1, STAT1, and PIK3R2 proteins. However, it is known that STAT1 plays a role in controlling CXCL1 expression [26]. On the other hand, specific inhibition of PI3K/Akt abolished serine-dependent STAT1 phosphorylation and reduced STAT1-dependent gene transcription and expression approximately 7-fold [27]. Based on these reasons, the activity of the PIK3R2 protein complex (PI3Ks) will be used as a target for inhibition by compounds in tea leaves (*C. sinensis* var. *assamica*).

The correlation coefficient value (R-square, R^2) of the graph between the predicted log(IC_{50}) and the actual log(IC_{50}) of the PI3-kinase class I (PI3Ks) complex inhibitor compound is presented in **Figure 4**. The figure shows that the R-squared value (R^2) = 0.5263 was obtained for the PI3Ks inhibitor prediction model. Thus, the LogIC_{50} prediction model based on the SkelSpheres descriptor with the SVR method is considered valid [19]. Furthermore, the prediction model was used to predict the LogIC_{50} of compounds (natural products) from tea leaves (*C. sinensis* var. *assamica*). The prediction results are presented in **Table 4**.

Table 2. Key genes related to inflammatory pathways and their fold change (FC) values.

Gene	Log2FC (acne_lesion vs non-acne)	Pathway	Connected pathway
CCL4	1.222	*Cytokine-cytokine receptor interaction, Chemokine signaling pathway, NF-kappa B signaling pathway, Toll-like receptor signaling pathway*	4
CXCL1	3.625	*Cytokine-cytokine receptor interaction, Chemokine signaling pathway, NF-kappa B signaling pathway, IL-17 signaling pathway, TNF signaling pathway, NOD-like receptor signaling pathway,*	6
CXCL2	2.453	*Cytokine-cytokine receptor interaction, Chemokine signaling pathway, NF-kappa B signaling pathway, IL-17 signaling pathway, TNF signaling pathway, NOD-like receptor signaling pathway,*	6
CXCL8	3.269	*Cytokine-cytokine receptor interaction, Chemokine signaling pathway, NF-kappa B signaling pathway, Toll-like receptor signaling pathway, IL-17 signaling pathway, NOD-like receptor signaling pathway,*	6
IL1B	0.942	*Cytokine-cytokine receptor interaction, NF-kappa B signaling pathway, Toll-like receptor signaling pathway, IL-17 signaling pathway, TNF signaling pathway, NOD-like receptor signaling pathway, MAPK signaling pathway*	7
MYD88	0.475	*NF-kappa B signaling pathway, Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, MAPK signaling pathway*	4
PIK3R1	-0.614	*Chemokine signaling pathway, Toll-like receptor signaling pathway, TNF signaling pathway, JAK-STAT signaling pathway*	4
PIK3R2	1.582	*Chemokine signaling pathway, Toll-like receptor signaling pathway, TNF signaling pathway, JAK-STAT signaling pathway*	4
STAT1	1.03	*Chemokine signaling pathway, Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, JAK-STAT signaling pathway*	4
TRAF3	0.467	*NF-kappa B signaling pathway, Toll-like receptor signaling pathway, IL-17 signaling pathway, TNF signaling pathway, NOD-like receptor signaling pathway*	5

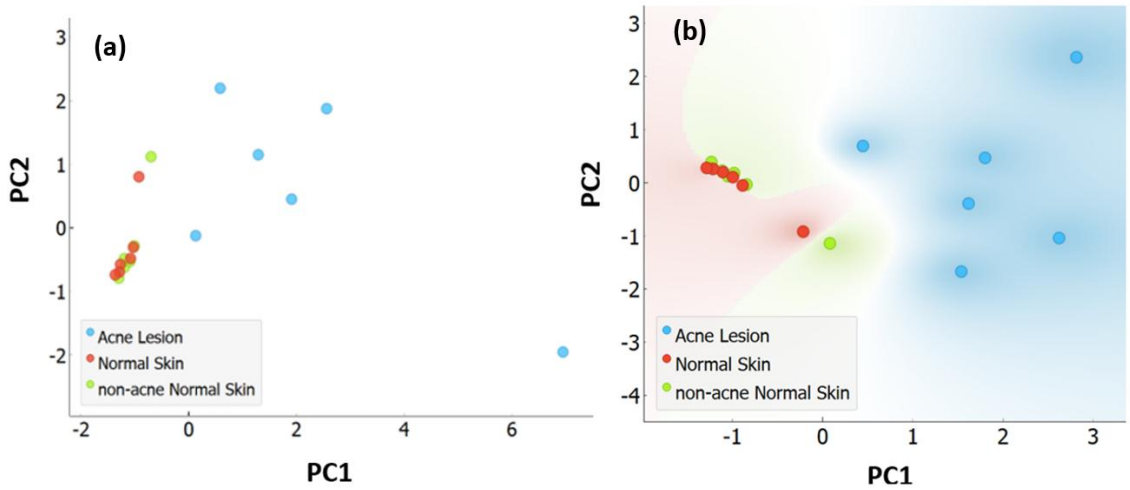

Figure 3. PCA analysis based on the expression of key inflammation-related genes: 6 DEGs (a) and 3 DEGs (b).

Table 3. Confusion matrix (predicted vs actual) of key inflammation-related gene expression values

		Predictiom 6DEGs/3DEGs			
		Acne lesion	**normal skin**	**Non-acne**	∑
Actual 6DEGs/3DEGs	acne lesion	5/6	1/0	0	6/6
	normal skin	0	3/4	3/2	6/6
	Non-acne	0	4/0	2/6	6/6
	∑	5/6	8/8	5/4	18/18

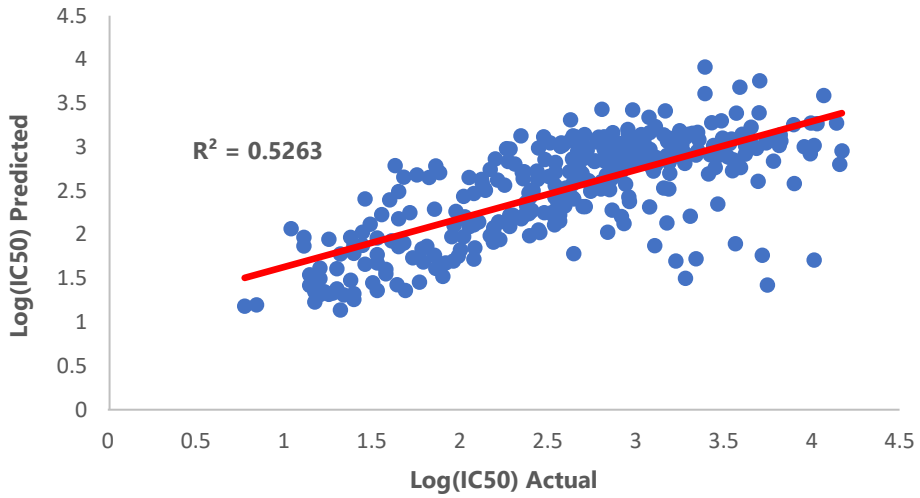

Figure 4. Validation of compound prediction models on the ChEMBL database as PI3Ks inhibitors.

Table 4. Results of the prediction of compound activity in tea leaves (*C. sinensis* var. *assamica*) as inhibitors of PI3Ks

Activity number	Compounds	CID	IC_{50}, µM	Criteria[27]
1	4-Guanidinobutyric acid	500	1.125	*good activity*
2	2-Methylbenzothiazole	8446	1.133	*good activity*
4	(2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-chromen-4-one	667495	1.214	*good activity*
5	(2R)-5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-chromen-4-one	667495	1.214	*good activity*
7	Assamsaponin F	10677946	1.275	*good activity*
8	Assamsaponin F	10677946	1.275	*good activity*
22	Floratheasaponin A	44566564	1.276	*good activity*
24	Desacyl-theasaponin E	10843814	1.278	*good activity*
37	9-beta-D-Ribofuranosylxanthine	1189	1.301	*good activity*
38	Xanthosine	64959	1.301	*good activity*
39	Procyanidin B3	146798	1.311	*good activity*
40	Procyanidin B3	146798	1.311	*good activity*
41	Caffeine	2519	1.320	*good activity*

The 41 natural products in *C. sinensis* var. *assamica* obtained from PubChem all met the criteria for 'good activity' with IC_{50} = 1-20 μM [28]. Xanthine compounds such as caffeine and theobromine have anti-inflammatory and anti-microbial properties, two activities that affect acne growth [29]. Meanwhile, procyanidin is known to have antioxidant properties, which are also important in influencing the development of acne [30]. In addition to its potential as an anti-inflammatory, antioxidant, and antimicrobial, in silico tests in this study indicate that compounds in tea leaves (*C. sinensis* var. *assamica*) can also be PI3Ks inhibitors. Anti-acne activity is known to work by inhibiting the PI3K-Akt signaling pathway and mitochondrial activity, as seen in licorice compounds [31]. Meanwhile, *C. acnes* induces apoptosis, such as in nucleus pulposus cells (NPC), through the PI3K and mTOR pathways [32]. Thus, further research on anti-acne tea leaves (*C. sinensis* var. *assamica*) can be conducted by targeting the PI3K-Akt signaling pathway.

4. CONCLUSIONS

This study successfully identified several genes related to the inflammatory pathway in acne, including CCL4, CXCL1, CXCL2, CXCL8, IL1B, MYD88, PIK3R1, PIK3R2, STAT1, and TRAF3, with CXCL1, STAT1, and PIK3R2 highlighted as potential biomarker candidates. In silico analysis of compounds in tea leaves (*C. sinensis* var. *assamica*) showed that 41 natural product compounds, including theobromine, assamsaponin, procyanidin, and caffeine, have the potential to act as inhibitors of the PI3K/Akt pathway that plays a role in acne pathogenesis. The predicted activity of these compounds provides initial evidence that tea leaves (*C. sinensis* var. *assamica*) may be an effective therapeutic agent in treating acne. Further studies are needed to validate these findings in vitro and in vivo.

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