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ORIGINAL RESEARCH

Metabolomic Profiling Reveals Distinct Plasma Metabolic Signatures in Acne Patients with and without Depression

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Background: Acne vulgaris is common and often accompanied by depression, but their linking mechanisms remain unclear. Metabolomic profiling helps identify biomarkers and perturbed pathways, so this study explores metabolic associations/pathways in acne comorbid with depression via untargeted metabolomics.

Methods: Seventy-four acne patients were grouped by Patient Health Questionnaire-9 (PHQ-9) scores (≥10: depressive, n=21; <10: non-depressive, n=53). Their plasma was pretreated with cold methanol/acetonitrile, analyzed via Agilent 1290 Ultra-High Performance Liquid Chromatography (UHPLC)-AB Triple TOF 6600 Liquid Chromatography-Mass Spectrometry (LC-MS). Data were processed by XCMS; metabolites annotated via Human Metabolome Database (HMDB)/METLIN. Principal Component Analysis (PCA), Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were used.

Results: We identified differential metabolites using Fold Change (FC) analysis combined with statistical significance testing, defining those with FC > 1.5 (upregulated) or FC < 0.67 (downregulated) and $p < 0.05$ as significant. Volcano plots and hierarchical clustering heatmaps clearly visualize these metabolites, showing distinct clustering patterns that distinguish the two groups. OPLS-DA modeling further revealed 24 key differential metabolites (VIP > 1 and $p < 0.05$), including 16 in positive ion mode (eg, hypoxanthine, taurine, L-tryptophan) and 8 in negative ion mode (eg, L-ascorbic acid, palmitic acid). Notably, Clustering patterns aligned with these metabolites (eg, upregulated hypoxanthine, downregulated L-ascorbic acid), confirming reliable differences. KEGG annotated 41 core pathways, with protein digestion and absorption (lowest p-value, annotated with 7 key amino acids) as a top-ranked pathway. Five amino acid metabolism-related pathways were upregulated, indicating enhanced amino acid turnover in acne patients with depression; all metabolites in the protein digestion and absorption pathway were also upregulated in this group.

Conclusion: Hypoxanthine, taurine and branched-chain amino acids may be biomarkers for acne-depression comorbidity. Protein digestion/absorption could be a new prognostic marker/therapeutic target, with metabolic-neuroendocrine imbalance underlying the comorbidity.

Keywords: acne with comorbid depression, untargeted metabolomics, serum biomarkers, metabolic pathways

Introduction

Acne vulgaris is one of the most prevalent dermatological conditions worldwide, affecting individuals across various age groups and ethnicities.[1] Characterized by the presence of comedones, inflammatory lesions, and, in severe cases, scarring, acne can significantly impair an individual's quality of life.[2,3] Epidemiological studies estimate that approximately 85% of adolescents and young adults experience acne, with a notable prevalence persisting into adulthood.[4,5]

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Beyond its physical manifestations, acne is frequently associated with substantial psychological distress, including lowered self-esteem, anxiety, and depression.[6]

The psychosocial burden of acne extends its impact beyond dermatological health, highlighting the intricate interplay between skin conditions and mental health.[7] Depression, a common and debilitating mental disorder, has been increasingly recognized as a comorbid condition in individuals suffering from chronic acne.[8] The bidirectional relationship between acne and depression suggests that the chronic inflammation and persistent self-consciousness stemming from acne may contribute to the onset or exacerbation of depressive symptoms.[9] Conversely, depression can influence the perception and management of acne, potentially aggravating its severity through behavioral and physiological pathways.[10,11] Despite the established association between acne and depression, the underlying biological mechanisms linking these two conditions remain incompletely understood.

Metabolomics is an emerging field that involves the systematic identification and quantification of a wide range of metabolites in biological samples.[12] In recent years, it has become a powerful tool for investigating dynamic changes of small-molecule metabolites in living organisms and their associations with physiological and pathological processes. By analyzing metabolites such as amino acids and lipids, metabolomics can reveal disease-specific metabolic signatures and identify potential biomarkers.

Previous metabolomic studies have independently characterized the metabolic profiles of acne and depression. Acne patients exhibit dysregulated lipid metabolism, oxidative stress, and inflammatory responses,[13,14] whereas depression is associated with abnormalities in amino acid metabolism, impaired energy production, and neurotransmitter synthesis.[15] Notably, several metabolites involved in purine, amino acid, lipid, and bile acid metabolism have been found to be altered in both conditions, suggesting potential shared metabolic underpinnings. For example, hypoxanthine accumulates in acne as a marker of oxidative damage[16] and is also implicated in neuroinflammation in depression.[17] Similarly, decreased L-tryptophan exacerbates neuroinflammation in depression,[18] while microbiota-derived L-tryptophan metabolites promote skin barrier repair and function through activation of the aryl hydrocarbon receptor (AHR) signaling pathway.[19] Although no studies have yet directly demonstrated that gut microbial metabolites such as phenylacetic acid and DL-indole-3-lactic acid influence acne or depression via the gut–skin–brain axis, the antioxidant activity of trans-2-hydroxycinnamic acid highlights oxidative stress as a common pathological bridge and potential therapeutic target. Together, these findings underscore the value of metabolomics in elucidating the mechanisms underlying acne–depression comorbidity.

Despite these advances, few studies have systematically investigated the shared metabolic features of patients with both acne and depression, leaving a significant gap in understanding the mechanisms of their comorbidity. To address this gap, the present study aims to perform comprehensive metabolomic profiling of plasma samples from acne patients with and without comorbid depression. By employing advanced analytical techniques such as mass spectrometry and nuclear magnetic resonance spectroscopy, we seek to identify unique metabolic signatures that characterize the interaction between acne and depression. The findings are expected to reveal both shared and distinct metabolic pathways, provide potential biomarkers for early detection, and identify novel therapeutic targets. Ultimately, this study aims to bridge the gap between dermatological manifestations and psychiatric symptoms, promoting an integrated patient care approach that addresses both physical and mental health.

Materials and Methods

Participants and Sample Collection

Patients diagnosed with acne vulgaris based on the "China Acne Treatment Guidelines (2019 Revision)"[20] were recruited from the Department of dermatology in the Affiliated Hospital of Southwest Medical University from January 2021 to October 2021 in the study. The General Acne Grading System (GAGS score) was used to assess the severity of acne.[21] The Quality of Life-Acne (QoL-Acne) was applied to evaluate the life quality of all acne patients, This QoL-Acne scale has been validated domestically.[22,23] Depression was assessed using the 9-item Patient Health Questionnaire (PHQ-9),[24] a depression screening scale based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The Chinese version of the PHQ-9 used in this study has undergone linguistic validation and demonstrated good

psychometric properties.[25,26] A score of ≥10 on the PHQ-9 indicates depression in a patient. In this study, individuals were divided into experimental (PHQ-9 ≥10, acne with depression) and control (PHQ-9 <10, acne without depression) groups based on PHQ-9 scores.

Exclusion criteria included: ①patients with acne vulgaris who have previously taken retinoids; ②patients with severe infections, cardiovascular and cerebrovascular diseases, hepatic and renal insufficiency, diabetes mellitus or other endocrine diseases, gastrointestinal diseases, etc.; ③patients with psychiatric disorders other than depression; ④patients who have had antipsychotic treatments in the past, and those who have taken medications that may induce depressive moods. A total of 74 patients were finally included in this study, of which, 53 patients were diagnosed with acne, and 21 patients diagnosed with acne with depression.

Fasting blood samples were collected from all participants using EDTA tubes. Plasma was separated by centrifugation at 3000 rpm for 10 minutes at 4°C and stored at −80°C until metabolomics analysis.

Ethics Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Affiliated Hospital of Southwest Medical University (approval number: [KY2023426]). Written informed consent was obtained from all participants or guardians prior to their enrollment in the study. Participants were informed about the study objectives, procedures, potential risks, and benefits, and were assured of their right to withdraw from the study at any time without any consequences. All data were anonymized to protect participant confidentiality, and access to the data was restricted to authorized researchers only.

Non-Targeted Metabolomics Sequencing

Plasma samples were pretreated by protein precipitation using cold methanol/acetonitrile (4:1, v/v), followed by centrifugation to remove proteins. The supernatant containing metabolites was dried and reconstituted in a water/acetonitrile mixture (1:1) for analysis. Chromatographic separation was performed on an Agilent 1290 Infinity LC UHPLC system equipped with a C18 column (2.1 × 100 mm, 1.7 μm) using a gradient elution of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) for positive ion mode, or 10 mM ammonium acetate (pH 9.0) (A) and acetonitrile (B) for negative ion mode. Quality control (QC) samples, pooled from all experimental samples, were injected at regular intervals to monitor system stability. Metabolite detection was carried out on an AB Triple TOF 6600 mass spectrometer with electrospray ionization (ESI) in both positive and negative modes. Full-scan MS data (m/z 50–1200) and data-dependent MS/MS acquisition were performed to capture metabolite profiles and fragmentation patterns. Raw data were processed using XCMS for peak alignment, and metabolites were annotated by matching against HMDB and METLIN databases based on accurate mass and MS/MS spectra.

Metabolomics Data Analysis

To ensure data quality, multiple validation approaches were employed. PCA demonstrated tight clustering of QC samples in both positive and negative ion modes, indicating minimal technical variability. Pearson correlation analysis further confirmed high reproducibility ($r > 0.9$ for QC samples). Robustness was validated via Hotelling's T2 test, where all QC samples fell within the 99% confidence interval, and multivariate control charts showed fluctuations within ±3 standard deviations. Additionally, Relative Standard Deviation (RSD) analysis revealed that >85% of metabolic features in QCs had RSD ≤ 30%, confirming system stability. For group comparisons, univariate analysis (Fold Change [FC] with volcano plots) and multivariate analysis (PCA, PLS-DA, and OPLS-DA) were applied to identify significantly altered metabolites (VIP >1.0, $p < 0.05$). Correlation heatmaps visualized metabolite relationships, while Fisher's exact test and pathway enrichment analysis (bubble plots) highlighted perturbed metabolic pathways. Together, these methods ensured rigorous data reliability and biological interpretation.

Statistical Analysis

Continuous variables data were presented as mean ± standard deviation (SD). Group differences were evaluated using t-tests. Categorical variables data were summarized as frequencies (percentages). Differences between groups were

assessed using Pearson's chi-square test or Fisher's exact test (if expected cell counts were <5). Statistical significance was defined as a two-tailed p-value < 0.05. All analyses were performed using SPSS (version 29.0.2.0).

Results

Clinical Characteristics of Acne Patients with and without Depression

To evaluate whether there were baseline differences in clinical features between acne patients with and without depression (which might affect subsequent metabolomic results), we first compared the demographic and clinical data of the two groups. A total of 74 patients with acne vulgaris were enrolled in this study, with equal gender distribution (37 males and 37 females). Specifically, 21 patients were diagnosed with acne accompanied by depression (8 males, 13 females), and the remaining 53 patients had acne without depression (29 males, 24 females). No statistically significant differences were observed between the two groups in terms of gender, age, marital status, childbearing history, sleep quality, body mass index (BMI), place of residence, family history of acne, smoking status, or drinking history (all p-values > 0.05). This indicated that the baseline characteristics of the two groups were balanced, and the subsequent metabolomic differences could be attributed to the presence or absence of depression rather than other confounding factors (Supplementary Table 1).

Metabolite Identification and Attribution Classification

To clarify the overall plasma metabolite profile of the study population, we performed structural identification of metabolites using a local database, and further classified the identified metabolites by their chemical attributes. Specifically, metabolite structural identification was conducted by matching retention time, molecular mass, and collision energy with entries in the local metabolomic database. A total of 346 metabolites were identified across both positive and negative ion modes, including 221 in positive ion mode and 125 in negative ion mode. The chemical classification of these metabolites was as follows: 59 lipid and lipid-like molecules (17.05%), 56 organic acids and their derivatives (16.19%), 26 organic heterocyclic compounds (7.51%), 15 nucleosides, nucleotides, and analogs (4.34%), 15 organic oxygenated compounds (4.43%), 13 benzene ring-type compounds (3.76%), 9 organic nitrogen compounds (2.60%), 6 saccharide polyketides (1.73%), 1 organic oxygenated molecule (0.29%), and 1 organosulfur compound (0.29%). Lipids and organic acids were the two most abundant metabolite classes, accounting for more than 30% of the total identified metabolites, which is consistent with the previous finding that lipid metabolism disorders are closely associated with acne, but our study further expanded this observation to the acne population with depression (Supplementary Figure 1).

Analysis of differences Between Groups

To investigate whether there are distinct metabolic profiles between acne patients with and without depression, we performed a series of multivariate statistical analyses followed by screening of differential metabolites and their functional characterization.

Multivariate Statistical Analysis

We first conducted PCA to observe the overall distribution pattern of samples in positive and negative ion modes. The PCA score plots revealed partial overlap between the two groups in both ion modes, indicating limited discrimination power of this unsupervised method. Given this, we employed PLS-DA, a supervised multivariate statistical method, which showed better separation between the two groups in both ion modes.

To further eliminate irrelevant variations and enhance the reliability of group discrimination, we applied OPLS-DA. The OPLS-DA score plots demonstrated clear separation without overlap between the acne with depression group and acne without depression group in both positive and negative ion modes, indicating distinct metabolic profiles associated with depressive status in acne patients. This robust discrimination is noteworthy as it represents the first evidence, to our knowledge, of a specific metabolic signature linked to comorbid depression in acne patients (Supplementary Figure 2).

Screening of Differential Metabolites

We further identified differential metabolites by combining FC analysis with statistical significance testing. Metabolites with FC > 1.5 (upregulated) or FC < 0.67 (downregulated) and p-value < 0.05 were considered significantly differential. The distribution of these differential metabolites is visualized in volcano plots and hierarchical clustering heatmaps (Figure 1), clearly showing distinct metabolic patterns between the two groups.

Bioinformatics Analysis of Differential Metabolites

Using OPLS-DA modeling, we calculated Variable Importance in Projection (VIP) values for each metabolite to evaluate their contribution to group separation. A total of 24 metabolites were identified as key differential metabolites based on the criteria of VIP > 1 and p-value < 0.05. These included 16 metabolites from the positive ion mode: hypoxanthine, tyramine, phenyl lactic acid, L-methionine, L-glutamate, erucamide, taurine, L-threonine, L-tryptophan, glycine deoxycholic acid, L-leucine, DL-indole-3-lactic acid, L-arginine, trans-2-hydroxycinnamic acid, and D-proline; and 8 metabolites from the negative ion mode: D-aspartic acid, DL-lactate, L-ascorbic acid, 2-oxo adipic acid, L-gulonic-gamma-lactone, palmitic acid, taurochenodeoxycholate, and allantoin (Table 1).

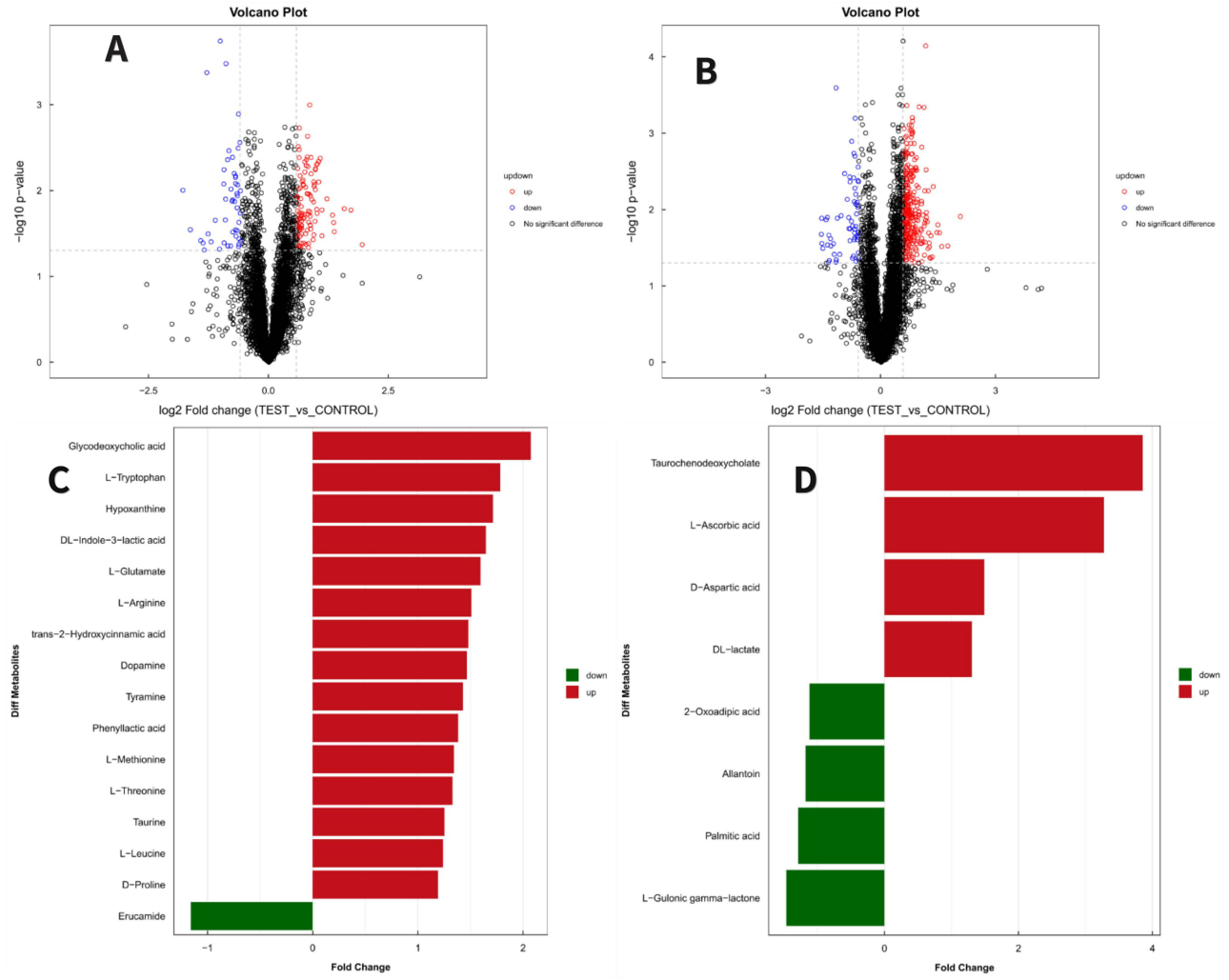

Figure 1 Difference metabolite plot.

Notes: Figure (**A** and **B**) (A positive ion mode B negative ion mode) shows the volcano difference metabolite plot, with the horizontal coordinate being the multiplicity of difference expression log2 and the vertical coordinate the significance P value log10. Metabolites with FC > 1.5 and P value < 0.05 are shown in rose, while those with FC < 0.67 and P value < 0.05 are shown in blue, indicating upward and downward modifications. Metabolites in black are not significantly different. Figure (**C** and **D**) (C positive ion mode D negative ion mode) shows fold change analysis of significantly distinct metabolite expression. Horizontal coordinates show differential expression fold change, with red indicating greater than one and green indicating less than 1. Vertical coordinates show significant metabolites for differentiation.

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Table 1 Significant Different Metabolites Under Positive and Negative Modes

Mode	Name	VIP	p Value
Positive	Hypoxanthine	22.177	0.001
	Tyramine	8.282	0.002
	Phenyllactic acid	1.053	0.003
	L-Methionine	1.327	0.004
	L-Glutamate	2.449	0.004
	Erucamide	2.362	0.009
	Taurine	4.32	0.009
	L-Threonine	1.029	0.014
	L-Tryptophan	2.399	0.018
	Glycodeoxycholic acid	1.458	0.019
	L-Leucine	3.574	0.022
	DL-Indole-3-lactic acid	1.222	0.023
	L-Arginine	1.631	0.035
	Trans-2-Hydroxycinnamic acid	1.34	0.036
	D-Proline	3.671	0.039
	Dopamine	1.265	0.04
Negative	D-Aspartic acid	1.298	0.013
	DL-lactate	11.8	0.016
	L-Ascorbic acid	3.126	0.017
	2-Oxoadipic acid	7.735	0.024
	L-Gulonic-gamma-lactone	1.079	0.031
	Palmitic acid	9.282	0.04
	Taurochenodeoxycholate	2.181	0.043
	Allantoin	1.787	0.045

Notably, several of these differential metabolites (including tryptophan, taurine, and ascorbic acid) are involved in pathways related to neurotransmitter synthesis and oxidative stress regulation, which have not previously been linked specifically to acne-depression comorbidity. This finding provides novel insights into the potential biological mechanisms connecting acne and depression, distinguishing our work from previous studies that focused solely on acne pathophysiology without considering psychological comorbidities.

Correlation Analysis of Significantly Differential Metabolites

To explore potential relationships between metabolic perturbations and depressive symptoms, we performed correlation analyses between significantly differential metabolites and depression-related assessment scores, as well as inter-metabolite correlations.

Correlations Between Differential Metabolites and Clinical Assessment Scores

We first analyzed the correlations between five depression-related assessment scores and the 24 significantly differential metabolites identified earlier. Specifically, we examined associations with the 9-item Patient Health Questionnaire (PHQ-9), 7-item Generalized Anxiety Disorder Scale (GAD-7), and Athens Insomnia Scale (AIS) scores.

Statistical analysis revealed consistent correlation patterns across these three scales: significant negative correlations were observed with 2-oxo adipic acid, palmitic acid, and L-gulonic-gamma-lactone, while significant positive correlations were found with hypoxanthine, L-tryptophan, and L-methionine. Other metabolites exhibited varying degrees of positive correlations or no significant associations with these assessment scores (Figure 2A).

Notably, the positive correlation between L-tryptophan (a key precursor of serotonin, a neurotransmitter involved in mood regulation) and PHQ-9 scores represents a novel finding that links metabolic perturbations in acne patients to

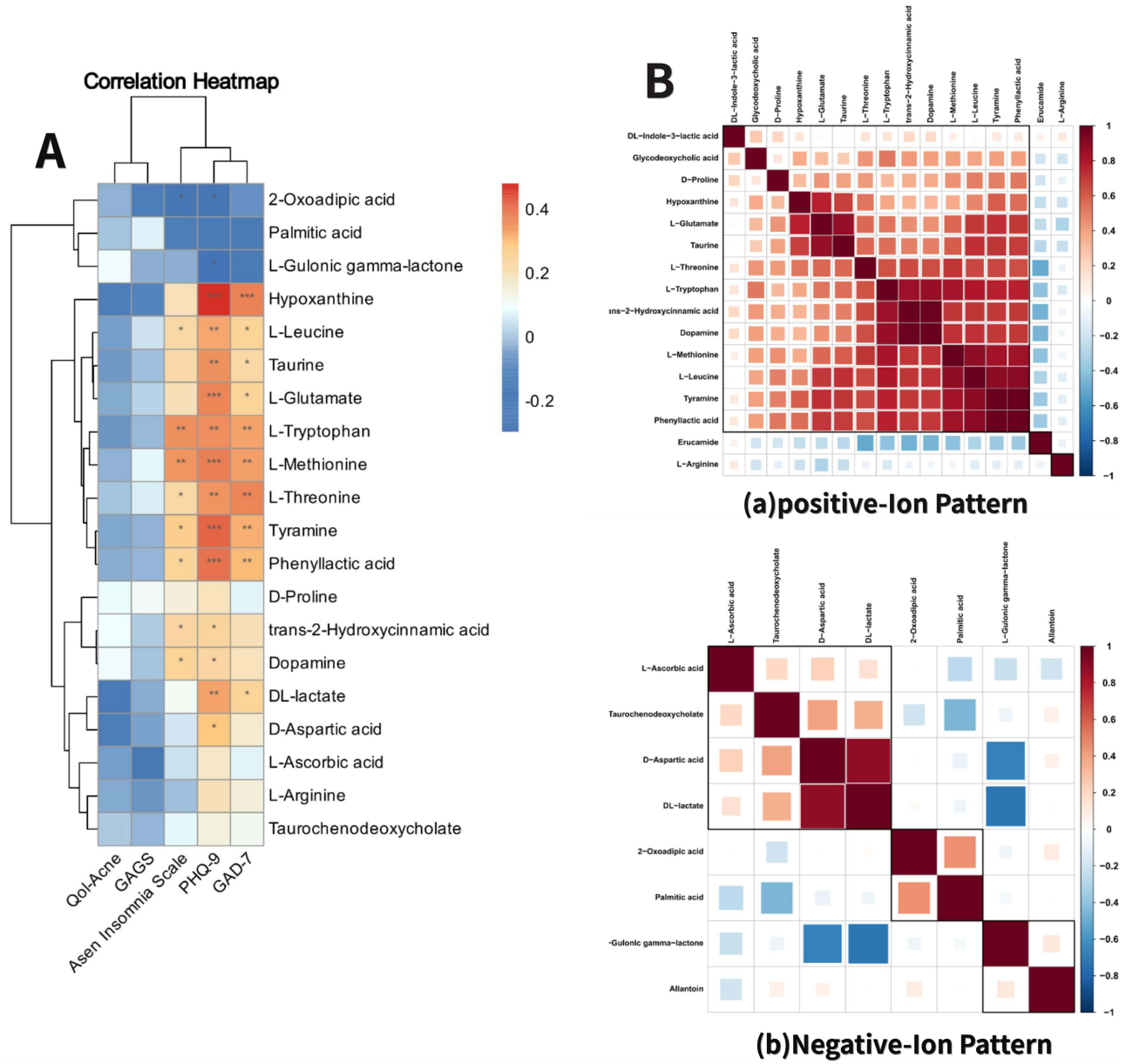

Figure 2 Correlation analysis.

Notes: (**A**) Heatmap of correlation analysis between depression ratings and significantly different metabolites. (**B**) (a positive ion mode b negative ion mode) Heatmap of correlation analysis between significantly different metabolites, Red indicates a positive correlation, blue indicates a negative correlation, and white indicates a non-significant association. The correlation coefficient's absolute value and color are linked. More correlation means a lower p-value and a larger square area.

potential neurochemical mechanisms underlying comorbid depression—this association has not been previously reported in acne research focusing on psychological comorbidities.

Inter-Metabolite Correlation Networks

To further clarify potential functional connections among the differential metabolites, we constructed a correlation heatmap to analyze their pairwise associations across both positive and negative ion modes (Figure 2B). In the positive ion mode, several prominent relationships emerged: erucamide and DL-indole-3-lactic acid showed a significant positive correlation, while L-arginine was also positively correlated with DL-indole-3-lactic acid; conversely, erucamide and L-arginine each exhibited negative correlations with other differential metabolites. Additionally, tyramine was significantly positively correlated with phenyl-lactic acid, whereas L-threonine was negatively correlated with erucamide. In

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the negative ion mode, DL-lactic acid and L-ascorbic acid (vitamin C) displayed a significant positive correlation, while L-gulonic-gamma-lactone—a metabolite involved in ascorbate metabolism—showed significant negative correlations with both DL-lactic acid and L-ascorbic acid. These inter-metabolite correlation patterns suggest potential disruptions in metabolic networks related to amino acid metabolism and antioxidant pathways in acne patients with depression. Together, these findings provide new insights into how metabolic perturbations are integrated in this comorbid condition, a relationship not previously systematically reported.

KEGG Enrichment Analysis of Differential Metabolic Pathways

To explore the biological functions of the 24 significantly differential metabolites and their potential roles in the comorbidity of acne and depression, we performed pathway enrichment analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. After mapping all differential metabolites to KEGG, 82 candidate metabolic pathways were annotated, from which 41 core pathways closely associated with the study groups were screened using Fisher's exact test. The top 20 most statistically significant pathways were visualized via bubble plots (Figure 3), among which the protein digestion and absorption pathway exhibited the lowest p-value and an enrichment factor of 0.15, and was annotated with seven key differential amino acids, including L-glutamate, L-arginine, L-methionine, L-tryptophan, L-leucine, L-threonine, and tyramine.

Further analysis revealed that five amino acid metabolism-related pathways—such as arginine and proline metabolism, leucine metabolism, and aspartate metabolism—showed upregulation of core amino acid metabolites, suggesting enhanced amino acid turnover in acne patients with depression. Differential abundance score plots indicated upregulation in four key pathways: protein digestion and absorption, central carbon metabolism in cancer, aminoacyl-tRNA biosynthesis, and amino acid biosynthesis (Figure 3). Notably, all metabolites within the protein digestion and absorption pathway were upregulated in the acne with depression group (Figure 4), supporting pathway activation. A metabolite–pathway interaction network was constructed to visually summarize these associations (Figure 5).

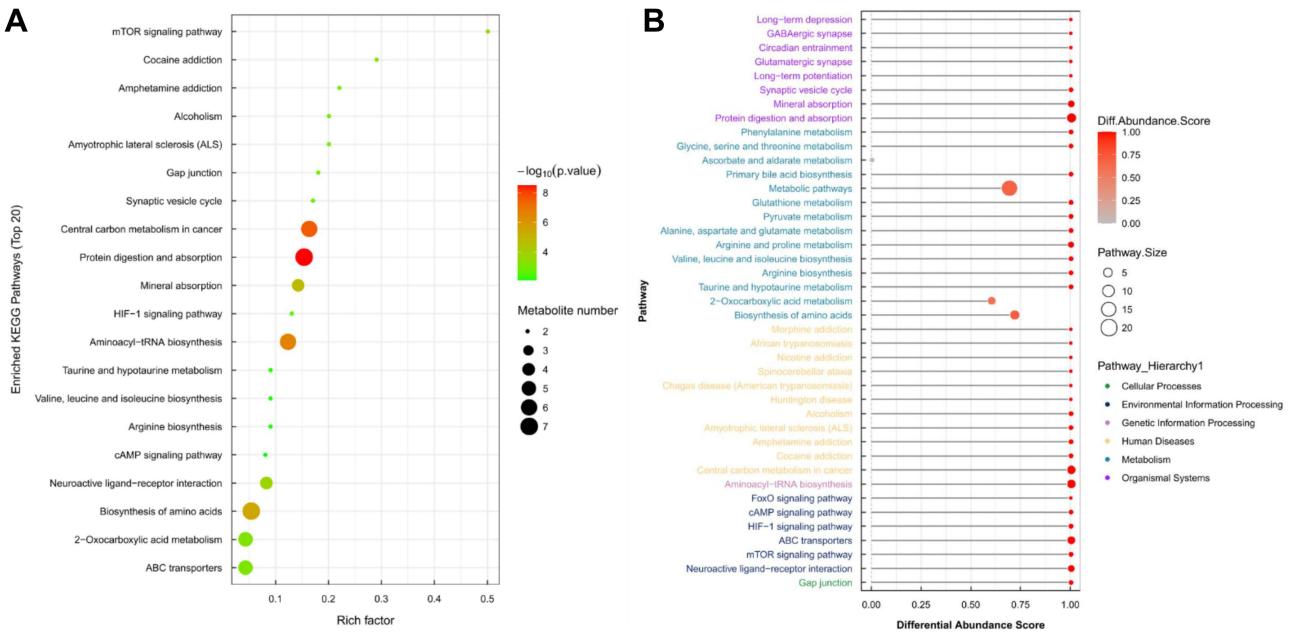

Figure 3 Differential abundance score map of all differential metabolic pathways.

Notes: (**A**) The pathway of KEGG enrichment The size of the pathway's effect factor is shown by the abscissa and bubble size in topological analysis. Each bubble represents a metabolic route. The ordinate of the bubble and its color (negative logarithm, or -log10 P value) indicates the enrichment analysis's P-value; the more significant the enrichment, the lower the P value. (**B**) Scores for each distinct metabolic pathway's differential abundance X-axis represents the differential abundance score (DA score), which displays the overall expression trend of all detected metabolites in the metabolic pathway. A score of 1 means that all identified metabolites in the route have an up-regulated expression trend. In contrast, a value of −1 means that all identified metabolites in the pathway have a down-regulated expression trend. The Y-axis represents the metabolic pathway's name. The size of the dot shows the number of metabolites in the line at the end; the more significant the dot, the more metabolites there are. The line segment's length indicates the DA score's absolute value. Higher levels of up-regulation of the pathway's overall expression are indicated by darker red, and lower levels of down-regulation are shown by darker blue.

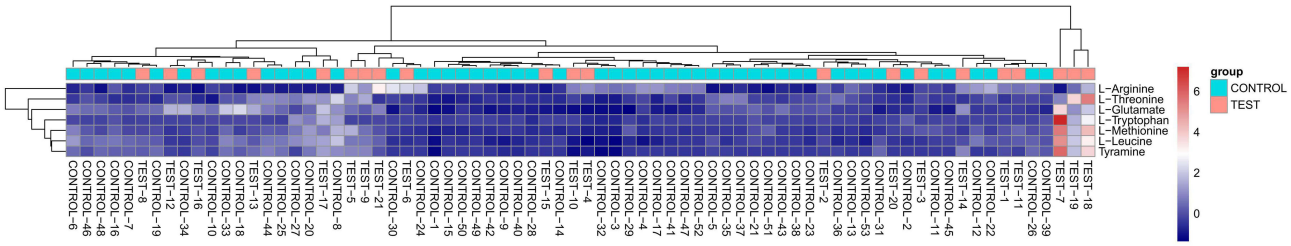

Figure 4 Metabolites clustering heat map of protein digestion and absorption pathway.
Notes: Red represents significantly different metabolites, blue indicates the KEGG pathway, a larger area indicates a higher interaction level, and a smaller area suggests a lower interaction level.

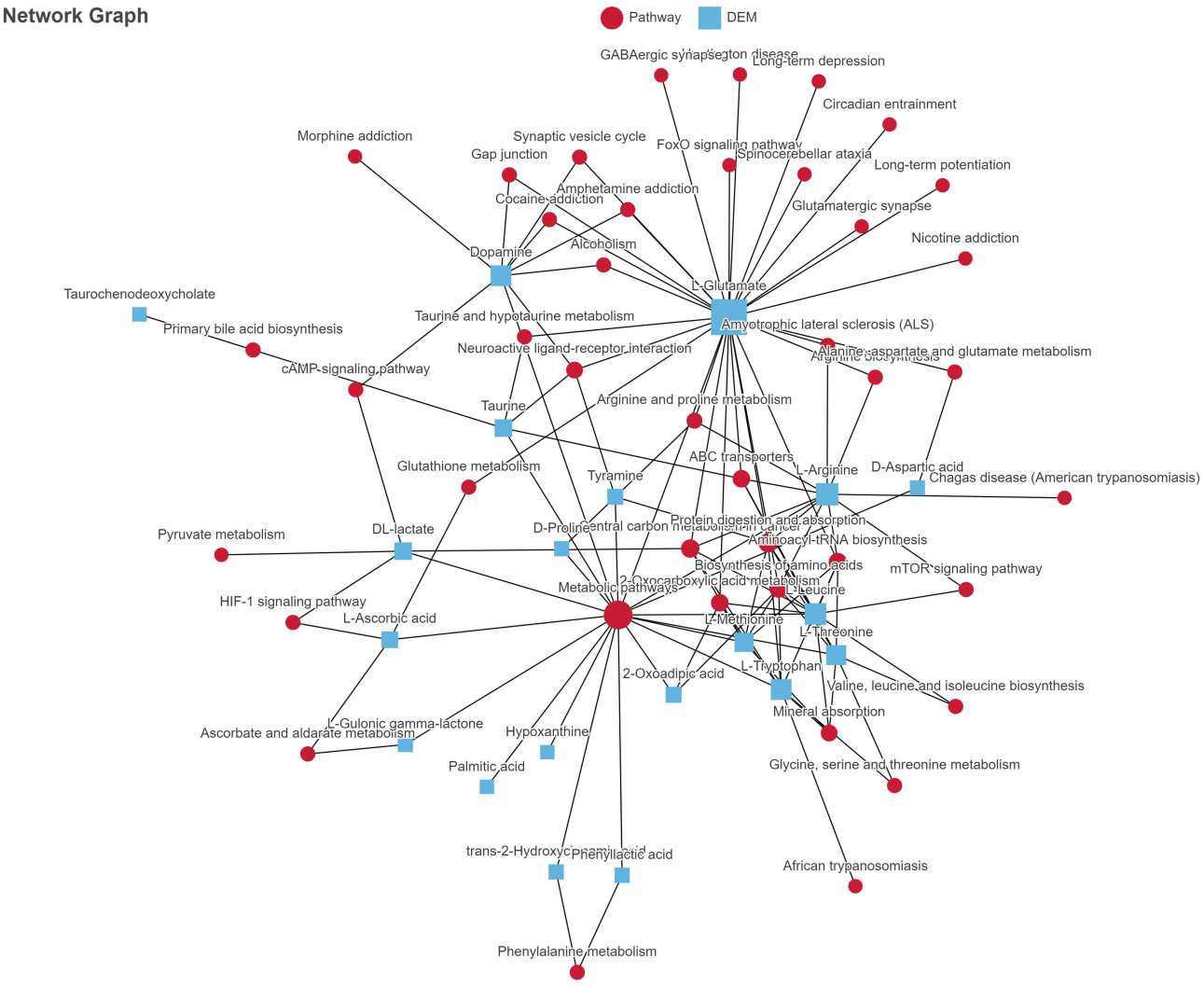

Figure 5 A metabolite–pathway interaction network.
Notes: Red circles stand for pathways, while blue squares represent differential metabolites (DEMs). The lines connecting the nodes signify the relationships, indicating that specific DEMs participate in the corresponding pathways. This network offers a visual summary of how altered metabolites are linked to diverse biological pathways, shedding light on the metabolic and pathway - level alterations associated with the condition under investigation.

A key novelty of this study is the identification of the protein digestion and absorption pathway as centrally disrupted in acne with depression. While prior research has separately linked specific amino acid metabolism to acne or depression, our findings first demonstrate that the integrated protein digestion and absorption pathway—along with its associated amino acid metabolites—is significantly upregulated in comorbid patients. This suggests that dysregulated protein

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nutrient utilization may be a distinctive metabolic feature of acne–depression comorbidity, offering a new functional perspective for understanding its pathology.

Discussion

This study provides the first comprehensive metabolomic profiling of acne vulgaris patients with and without comorbid depression. LC-MS/MS analysis of 74 patient samples (21 with depression comorbidity, 53 without) identified significant dysregulation in 24 metabolites, with hypoxanthine emerging as a pivotal differential metabolite. Pathway enrichment analysis revealed protein digestion and absorption as the most significantly altered metabolic pathway. These findings illuminate novel metabolic perturbations potentially underpinning the shared pathophysiological mechanisms of acne-depression comorbidity, particularly involving neuroendocrine signaling and inflammatory cascades.

In this investigation, the elevation of uric acid driven by hypoxanthine, insulin resistance induced by taurine, and hypoxia responses mediated by HIF-1α collectively constitute a metabolic triad central to the comorbidity of acne and depression. Among these, hypoxanthine emerges as the most critical biomarker, supporting Pu J. et al's meta-analysis identifying purine metabolites as candidate biomarkers in major depressive disorder.[27]

Hypoxanthine: The Energy and Oxidative Stress Gauge

Plasma hypoxanthine, a metabolic substance, functions as a precise gauge for both intra - and extracellular energy levels. It also serves as an early warning indicator of tissue free radical generation that occurs following hypoxia and reperfusion.[28] Elevated hypoxanthine levels trigger an increase in plasma uric acid. This rise in uric acid is closely associated with insulin resistance and dyslipidemia, which are well - recognized as significant contributing factors to acne.[29] Moreover, the insulin resistance resulting from heightened hypoxanthine levels has a dual - negative impact: it not only exacerbates acne but also elevates the risk of depression in acne patients.

Taurine: The Disruptor of Insulin Signaling

Park et al revealed that plasma taurine levels are elevated in depressed patients.[30] Further research by Park et al demonstrated that taurine, in a dose - dependent manner, reduces glucose absorption. It achieves this by down - regulating glucose transporter proteins 1 and 3 (GLUT1/3), which in turn increases the risk of insulin resistance in patients.[31] This finding establishes a direct metabolic link between taurine dysregulation and impaired insulin signaling, highlighting its role as another crucial component in the complex interplay between acne and depression.

HIF - 1α: The Convergence Point of Insulin Resistance and Hypoxia Signaling

Insulin resistance and hypoxia signaling converge through HIF - 1α to mediate the comorbidity of acne and depression. In acne: Sebum accumulation within the ducts induces ductal hypoxia.[32] This hypoxia activates HIF - 1α, which then exacerbates local inflammation and may further potentiate insulin resistance, creating a vicious cycle within the acne - affected tissue. In depression: Conversely, HIF - 1α dysregulation in the central nervous system (CNS) has detrimental effects. It disrupts the integrity of the blood - brain barrier and promotes neuroinflammation, both of which are mechanisms implicated in the development of depression.[33] Experimental evidence: Interestingly, experimental studies have shown that HIF - 1α activation can reverse depression - like behaviors in chronic unpredictable mild stress (CUMS) models.[34] This suggests that HIF - 1α plays a complex and dynamic role in the relationship between acne and depression.

The link between acne and Depression is mediated through neurotransmitter metabolism, inflammatory responses, and overall metabolic-neuroendocrine regulatory networks (Figure 6).Emerging evidence suggests that brain-derived neurotrophic factor (BDNF)may modulate neuroendocrine pathways, thereby contributing to the pathogenesis of acne and depressive symptoms.[35] BDNF may indirectly alter sebaceous gland secretion by altering hormonal homeostasis or metabolic processes, leading to acne.[36] In patients with depression, low levels of BDNF may lead to effects on neuronal signaling pathways downstream of it, including PI3K, MAPK, and PLCγ,[37] affecting neuronal functions such as dendritic remodeling and neurogenesis.[38] Chronic stress and depression may exacerbate this vicious cycle by reducing BDNF expression,[39] Critically, BDNF's PI3K/Akt signaling arm converges on mTOR targets (mTORC1/mTORC2) underlie Neurological Dysfunction,[40] leading to continued impairment of neuronal structure and function, including dendritic morphology and structural remodeling and neurogenesis. Although the signaling cascade of BDNF is not directly involved in the process of protein digestion and absorption, BDNF-mediated regulation of the nervous system may

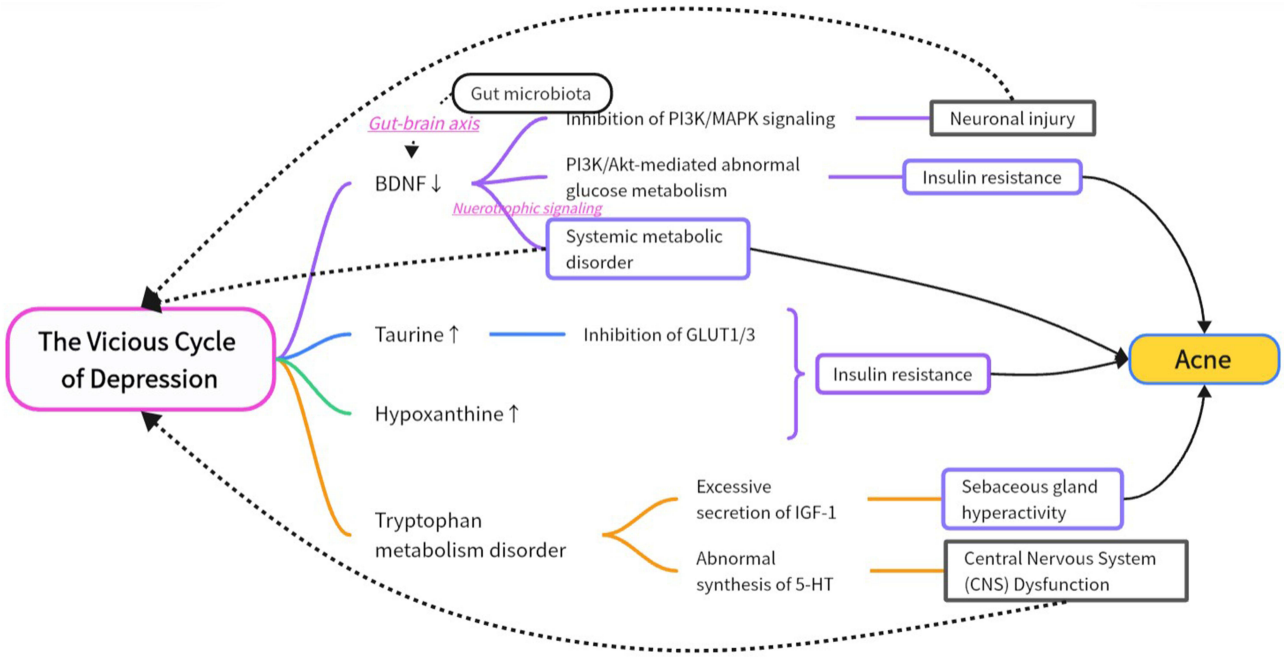

Figure 6 Shared Pathways in Acne and Depression: Gut-Brain-Metabolic Axis Dysregulation and Neuroendocrine Crosstalk.
Notes: Schematic illustration of the vicious cycle between depression and acne. Depression influences acne through multiple pathways: reduced brain-derived neurotrophic factor (BDNF, ↓) impacts gut microbiota, which in turn modulates signaling pathways (inhibiting PI3K/MAPK signaling to cause neuronal injury and mediating abnormal glucose metabolism via PI3K/Akt to induce insulin resistance); increased taurine (↑) inhibits GLUT1/3 to trigger insulin resistance; elevated hypoxanthine (↑) contributes to insulin resistance; and tryptophan metabolism disorder leads to excessive IGF-1 secretion (stimulating sebaceous gland hyperactivity) and abnormal 5-HT synthesis (causing CNS dysfunction). Conversely, acne can aggravate depression through these intermediate processes, forming a reciprocal vicious cycle. Arrows indicate the direction of influence; "↑" denotes an increase in the corresponding substance, "↓" denotes a decrease in the corresponding substance.

have an indirect effect on mTOR signaling integrates metabolic pathways through the neural-gut signaling pathway, mTOR critically governs keratinocyte differentiation and sebaceous gland function.[41,42] Hormonal drivers (androgens, growth factor 1(IGF-1), insulin) activate mTORC1 to induce acne.[43,44] In addition, the PI3K/Akt signaling arm of BDNF is closely associated with cellular metabolism and plays a key role in regulating glucose metabolism and maintaining energy homeostasis.[45] These observations collectively underscore a potential regulatory interface between neurotrophic signaling and systemic metabolic processes,[46] highlighting the need for mechanistic studies to dissect their bidirectional interactions in health and disease (Figure 6).

Our findings provide novel insights into the interplay between protein metabolism and dermatological/neurological disorders, Notably, tryptophan metabolism and its downstream metabolites serve as pivotal nodes in the biosynthesis of neurotransmitters and vitamins implicated in both depression and acne development. For instance, insulin-like IGF-1, a 70-amino-acid polypeptide containing tryptophan residues, IGF-1 specifically engaging the PI3K/Akt/FoxO1/mTORC1 axis,[47] has been extensively studied as a key mediator in acne pathogenesis.[48] Elevated tryptophan levels and associated metabolic intermediates may promote IGF-1 hypersecretion, thereby exacerbating sebaceous gland hyperactivity—a hallmark of acne vulgaris.[49] Additionally, emerging evidence highlights tryptophan as a critical precursor for both peripheral and central serotonin (5-hydroxytryptamine, 5-HT) synthesis.[50] A neurotransmitter modulating central nervous system (CNS) adaptive responses consistently implicated in depressive pathophysiology.[51] Collectively, these observations suggest that abnormalities within a shared metabolic-neuroendocrine axis underlie the comorbid presentation of acne and mood disorders.[52] This axis likely integrates dysregulated tryptophan metabolism with perturbations in other key pathways, such as the arginine-glutamate-GABA (Gamma-Aminobutyric Acid) axis. Specifically, aberrant metabolism within the arginine-glutamate-GABA pathway may interact reciprocally with dysfunctions in tryptophan metabolism, collectively driving pathological changes in both skin and neural systems to manifest the acne-depression comorbidity (Figure 7).

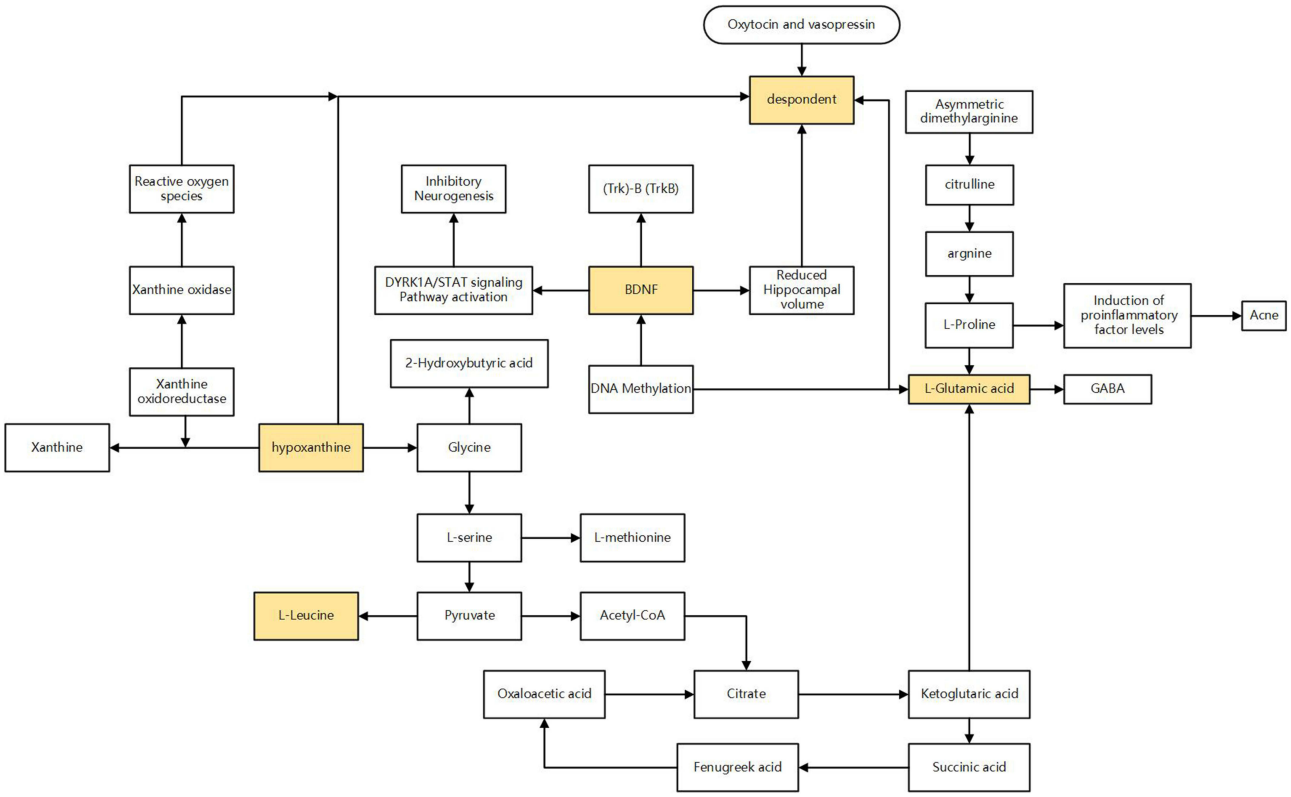

Figure 7 Metabolic pathways and their upstream and downstream relationships with the neuro-skin axis.
Notes: Key metabolites (yellow): Hypoxanthine (linked to ROS generation, xanthine oxidoreductase, glycine/L-serine interactions) and L-lactate (connected to pyruvate, acetyl-CoA, TCA cycle intermediates). Pathways include BDNF regulation (via DYRK1A/TAF1, affecting hippocampal volume), DNA methylation, and L-glutamic acid metabolism (linking to GABA and inflammation). Arrows denote metabolic flow/regulatory direction, converging on acne development.

Supporting this integrated view, we observed increased arginine, proline, and leucine metabolism. High plasma proline levels limit glutamate absorption and elevate pro-inflammatory cytokines, contributing to acne pathogenesis.[53] Meanwhile, elevated branched-chain amino acids may compete with precursor amino acids crucial for neurotransmitter synthesis, potentially impacting mental health.[54] Crucially, our pathway analysis unveiled that dysregulation within the arginine–glutamate–GABA axis serves as a direct catalyst for the induction of pro-inflammatory factors. Mechanistically, glutamate acts as a potent trigger, elevating pro-inflammatory cytokines, which drive acne pathogenesis. Importantly, this inflammatory axis extends beyond acne, impacting depression by activating microglia and disrupting neurotransmitter metabolism. This notion is further bolstered by glutamate signaling via (N-Methyl-D-Aspartic acid) NMDA receptors (NMDAR), which modulate mood and depression,[55] but also trigger an increase in IL-1α, subsequently leading to aberrant follicular keratinization in acne.[56]

Beyond acne, metabolomic studies in other dermatological conditions, such as psoriasis and atopic dermatitis, have also reported abnormalities in hypoxanthine levels and purine metabolism.[57,58] In parallel, epidemiological studies have consistently demonstrated elevated prevalence of depression in these chronic inflammatory skin diseases[59] Although no studies have directly examined whether hypoxanthine levels can predict depression comorbidity in non-acne dermatological populations, these converging lines of evidence support the broader relevance of our findings. Specifically, they suggest a potential shared link among purine metabolism, cutaneous inflammation, and heightened depression risk, underscoring the need for further investigation across multiple dermatological disorders.

Despite providing novel insights into the metabolic underpinnings of acne–depression comorbidity, the present metabolomics-based study has several limitations. While metabolomics has been widely used to investigate associations between depression and various comorbid conditions (eg, diabetes, gastrointestinal disorders, cancer), our study was restricted by a relatively small sample size and limited analytical platform, which precluded comprehensive profiling of

the full spectrum of metabolites. Moreover, the intricate interconnections among metabolites and metabolic pathways make it challenging to fully delineate their mechanistic contributions to comorbid depression. Therefore, while our findings highlight key metabolic axes—such as hypoxanthine-mediated purine metabolism, tryptophan and arginine–glutamate–GABA pathways, and neuroendocrine signaling—further research is required. Future large-scale and longitudinal clinical studies, including randomized controlled trials, are essential to confirm causality and evaluate potential metabolite-targeted interventions for the prevention or management of depression in patients with acne and other chronic inflammatory skin diseases.

Conclusion

In the present study, through in-depth exploration, hypoxanthine was successfully identified as a pivotal differential metabolite. Notably, KEGG enrichment analysis unveiled that the protein digestion and absorption pathway holds promise as a novel prognostic biomarker and a potential therapeutic target for acne vulgaris-associated depression, offering new perspectives for clinical management of this comorbidity. Subsequently, we delved into the key pathogenic mechanisms. It was found that elevated hypoxanthine levels lead to an increase in plasma uric acid, which in turn triggers insulin resistance and dyslipidemia, thereby promoting the development of acne. Concurrently, taurine exacerbates insulin resistance, further cementing the intricate link between acne and depression. Additionally, BDNF plays a regulatory role in both conditions via neuroendocrine pathways. Under chronic stress, reduced BDNF disrupts neuronal function through PI3K and MAPK signaling cascades and indirectly modulates systemic metabolism via the gut-brain axis, highlighting bidirectional crosstalk. Moreover, the mTOR signaling pathway serves as a central hub, with its abnormal activation being closely associated with sebaceous gland hyperactivity, insulin resistance, and neurological dysfunction.

Collectively, these findings firmly establish abnormalities in the metabolic-neuroendocrine axis as the common pathological underpinning for this comorbidity, providing a transformative framework for the development of targeted interventions and personalized treatment strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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