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Integrating mass spectrometry imaging and multi-omics strategies to reveal the mechanism of anti-inflammatory and anti-aging effects of Centella asiatica extract in skin

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1. Introduction

Centella asiatica (L.) Urban is a perennial herbaceous plant of the Centella genus in the Apiaceae family, commonly known as Gotu Kola, Indian Pennywort, or Tiger Grass. It is widely distributed in China, India, Southeast Asia and Africa, and has been used in Chinese traditional medicine for thousands of years. *Centella asiatica* has been extensively used to treat various skin diseases, including wounds, burns, scars, lupus, leprosy, eczema, psoriasis, and venous ulcers, ect [1-2]. Recent scientific studies have revealed that the the natural active ingredients in Centella asiatica exhibit anti-inflammatory, antibacterial, antifungal, antioxidant, anti-photoaging, anti-aging, and cell proliferation-promoting properties [3-4], making it a popular raw material in cosmetics. While numerous animal and cellular studies have explored the natural products and their dermatological effects, most research has focused on pentacyclic triterpenoids (such as asiaticoside, madecassoside, asiatic acid, and madecassic acid) [3-6]. There remains a lack of comprehensive analysis of Centella asiatica extract composition, and the molecular mechanisms underlying its skin benefits are not yet fully understood, requiring more systematic investigation.

In this study, cellular experiments demonstrated that Centella asiatica ethanol extract (CAE) possesses soothing, anti-wrinkle, and skin-tightening efficacy. Leveraging the LutMet-CM natural product database and the SkinEfficacyTarget database, along with LC-MS compositional analysis and network pharmacology, we conducted a thorough analysis of CAE's components and predicted its skin-related biological targets. Mass spectrometry imaging (MSI) was employed to examine the transdermal penetration of CAE active ingredients in ex vivo human skin. Finally, by integrating multi-omics analysis of CAE-treated cells, molecular docking, and spatial metabolomics data, we systematically elucidated the molecular mechanisms of CAE's soothing and anti-wrinkle effects. This study provides scientific evidences which support the application of Centella asiatica in the cosmetics industry.

2. Materials and Methods

Efficacy Evaluation Experiment, Component Analysis and Network Pharmacology

Centella asiatica was purchased from Bozhou Chinese Herbal Medicine Market in Anhui Province, originating from Anshun, Guizhou Province, and extracted with 70% ethanol. The efficacy evaluation experiment was set up with a normal control group, a model group (model induction only), a positive drug group, and low-, medium-, and high-dose CAE sample treatment groups. The histamine contents in mast cells were tested to evaluate the effect of

CAE on soothing skin [7]. The content of Type I collagen in fibroblasts supernatant was detected using the ELISA method, to assess anti-wrinkle and firming efficacy of CAE [8].

The component analysis of Centella asiatica extract was analyzed using a liquid chromatography-mass spectrometry system (ACQUITY UPLC I-Class HF coupled with QE high-resolution mass spectrometer) by OE Biotech Co., Ltd. (Shanghai, China) [9]. The SwissTargetPrediction platform and SkinEfficacyTarget database (OE Biotech) were used to predict the potential targets of CAE active components in network pharmacology analysis. And a computational docking strategy was employed to explore the mechanism of ligand-receptor interactions.

Transdermal Absorption and Mass Spectrometry Imaging (MSI)

Skin tissue was obtained from foreskins of surgical donors at Zhejiang Xiaoshan Hospital (approval number: EC-2024022001). The experiment was divided into a blank control group and an experimental group (treated with 5% Centella asiatica extract). Prior to mass spectrometry analysis, the sections were vacuum-dried at -20°C for half an hour, and adjacent sections were stained with hematoxylin and eosin (H&E) for backup.

The Mass Spectrometry Imaging (MSI) experiment employed AFADESI-MSI coupled with Q-Orbitrap mass spectrometry, using negative ion mode, and data were acquired using Thermo Xcalibur [10].

Multiomics Analysis

The transcriptomics, proteomics, and metabolomics analysis were conducted by OE Biotech Co., Ltd. (Shanghai, China) [11]. RNA was extracted using the TRIzol reagent (Invitrogen, CA, USA) and sequenced on an Illumina Novaseq 6000 platform; differential expression was analyzed using DESeq2 [23]. Proteomic analysis ere performed by an Nanoelute2 system (Bruker) that was coupled to a timsTOF HT mass spectrometer (Bruker Daltonics). An ACQUITY UPLC I-Class plus (Waters Corporation, Milford, USA) fitted with Q-Exactive mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) was used to analyze the metabolic profiling. All workflows included quality control, standardization, and statistical analysis.

3. Results

Efficacy Experiments

Mast cells are the primary effector cells involved in allergic reactions. Upon stimulation by allergens or pseudo-allergens, they undergo degranulation and release various bioactive mediators, such as the inflammatory mediator histamine, triggering a series of allergic symptoms [12]. In this study, C48/80 induction significantly increased histamine release in rat basophilic leukemia (RBL-2H3) cells. However, treatment with different doses of Centella asiatica extract (CAE) markedly suppressed histamine release in a dose-dependent manner (Fig. 1A). These results demonstrate that CAE possesses anti-histamine release activity, supporting its soothing efficacy in alleviating allergic responses.

Dermal fibroblasts synthesize fibrillar collagens (including types I, II, III, V and VI), and the formation of skin wrinkles is closely associated with impaired collagen synthesis and expression [13]. After UVA-induced damage, the levels of type I collagen in human dermal fibroblasts were significantly reduced. However, treatment with different doses of CAE dose-dependently restored type I collagen expression in fibroblasts. Notably, CAE's ability to promote type I collagen regeneration was even superior to that of the positive control, boswellic acid (Fig. 1B). This finding highlights CAE's potent anti-wrinkle and skin-firming effects, likely contributing to its efficacy in anti-aging skincare applications.

Component Analysis and Network Pharmacology Analysis

By utilizing the LC-MS technology platform in conjunction with a self-built natural product database (LuMet-CM), we identified 763 compounds in CAE, with the top 10 components in terms of content being Madecassoside, Terminolic acid, Asiaticoside B, Scheffoleoside A, Isochlorogenic acid A, Asiaticoside, Manninotriose, Madecassic acid, Fructo-oligosaccharide DP7/GF6, and Fructomaltose (Table 1). The total content of these top 10 components

accounted for 71%.

Table 1. Chemical components of *Centella asiatica* extract (top 10)

Formula	Metabolites	m/z	rt (min)	Ion mode	Relative content (%)	class
C48H78O20	Madecassoside	1019.506	5.386	NEG	22.78	Terpenes
C30H48O6	Terminolic acid	549.342	8.524	NEG	11.70	Terpenes
C48H78O20	Asiaticoside B	997.499	5.388	POS	9.31	Terpenes
C48H78O19	Scheffoleoside A	1003.511	5.800	NEG	9.14	Terpenes
C25H24O12	Isochlorogenic acid A	515.118	5.072	NEG	3.91	Phenylpropanoids
C48H78O19	Asiaticoside	981.504	5.798	POS	3.63	Terpenes
C18H32O16	Manninotriose	549.166	0.800	NEG	3.35	Carbohydrates and Glycosides
C30H48O6	Madecassic acid	487.342	8.477	POS	2.64	Terpenes
C42H72O36	Fructo-oligosaccharide DP7/GF6	1135.378	0.905	POS	2.37	Carbohydrates and Glycosides
C18H32O16	Fructomaltose	543.132	0.796	POS	2.24	Carbohydrates and Glycosides

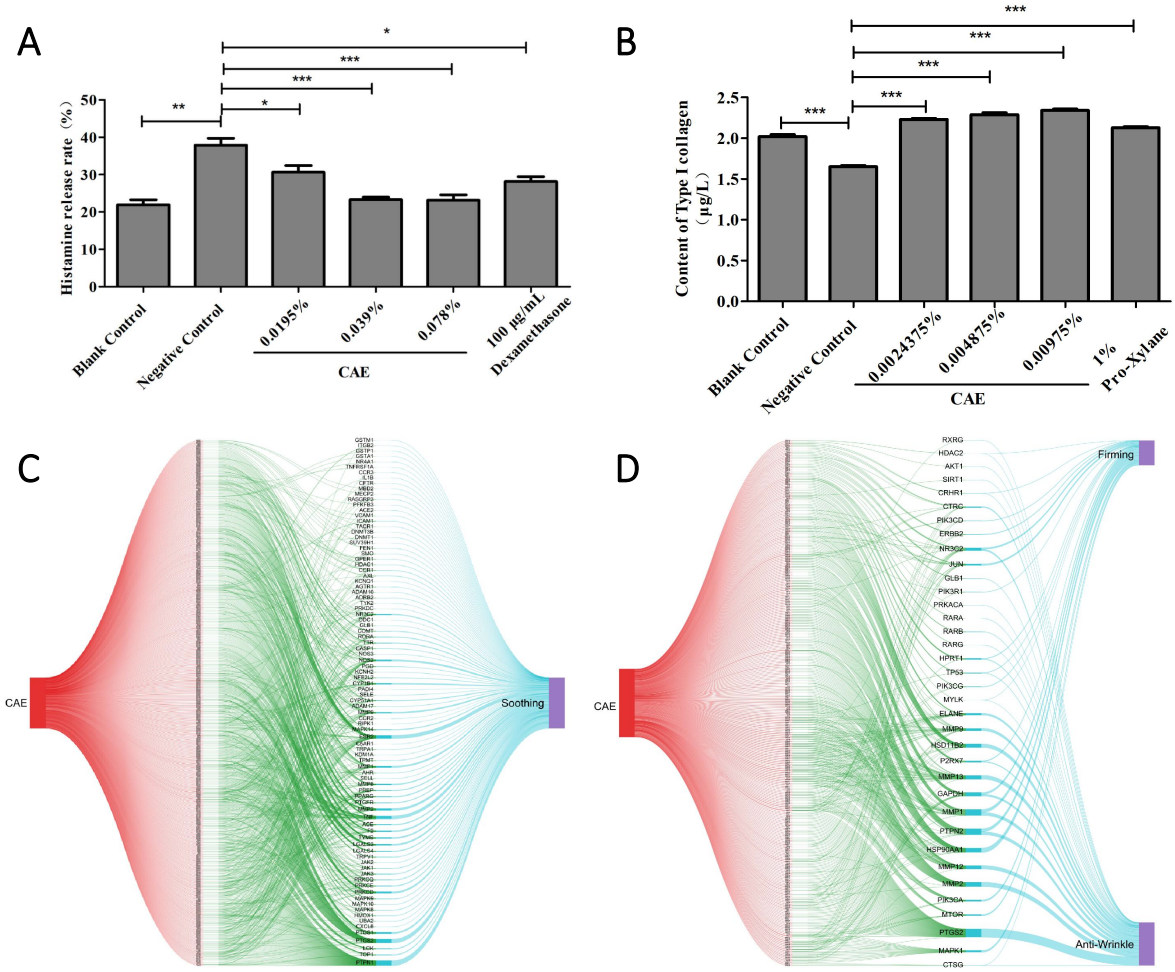

Figure 1. Efficacy of Centella asiatica Extract (CAE) and Network Pharmacology Analysis. A, Effect of CAE on histamine release in RBL-2H3 cells; B, Effect of CAE on type I collagen content in human fibroblasts; C, Sankey diagram of CAE components-targets-skin soothing efficacy; D, Sankey diagram of CAE components-targets-skin anti-wrinkle/firming efficacy.

Based on network pharmacology calculations and in combination with a self-built skin efficacy target database (SkinEfficacyTarget database), we obtained 90 intersection targets related to soothing efficacy and 36 intersection targets related to anti-wrinkle and firming efficacy. Sankey diagrams were employed to illustrate the relationships among CAE components, targets, and skin efficacy (Fig. 1C-D). The results indicated that the key targets associated with CAE components and skin soothing efficacy included MAPK14, PTGS1, PTGS2, TNF, JAK1, etc., with the functions of these proteins involving regulatory proteins on signaling pathways such as the TNF signaling pathway, IL-17 signaling pathway, and AGE-RAGE signaling pathway. The potential targets associated with CAE components and skin anti-wrinkle and firming efficacy included MMPs, TP53, PIK3R1, MAPK1, AKT1, MTOR, etc., involving multiple regulatory pathways (cAMP signaling pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, Jak-STAT signaling pathway, and Cellular senescence).

Mass Spectrometry Imaging

By applying CAE to ex vivo skin under cultured conditions and combining it with mass spectrometry imaging technology, we discovered that 12 components of CAE were transdermally absorbed into the skin tissue (Fig. 2). Among these, Luteolin, Morin, and Isorhamnetin were detected in the epidermis, while 12 components were detected in the dermis, namely: Luteolin, Morin, Isorhamnetin, Chlorogenic acid, Trifolin, Luteolin 7-O-glucuronide, 7-[(beta-D-Glucopyranosyl)oxy]-3',4',5,8-tetrahydroxyflavone, Miquelianin, Isochlorogenic acid A, 4,5-Di-O-caffeoylquinic acid methyl ester, Cellobiose, and Gentianose. Additionally, we detected 4 metabolites of CAE components in the skin, namely: Luteolin 4'-sulfate, 8-Hydroxyluteolin 8-sulfate, Isorhamnetin 7-O-sulfate, and Isorhamnetin 4'-O-glucuronide, with these metabolites being present in higher concentrations in the dermis (Fig. 2).

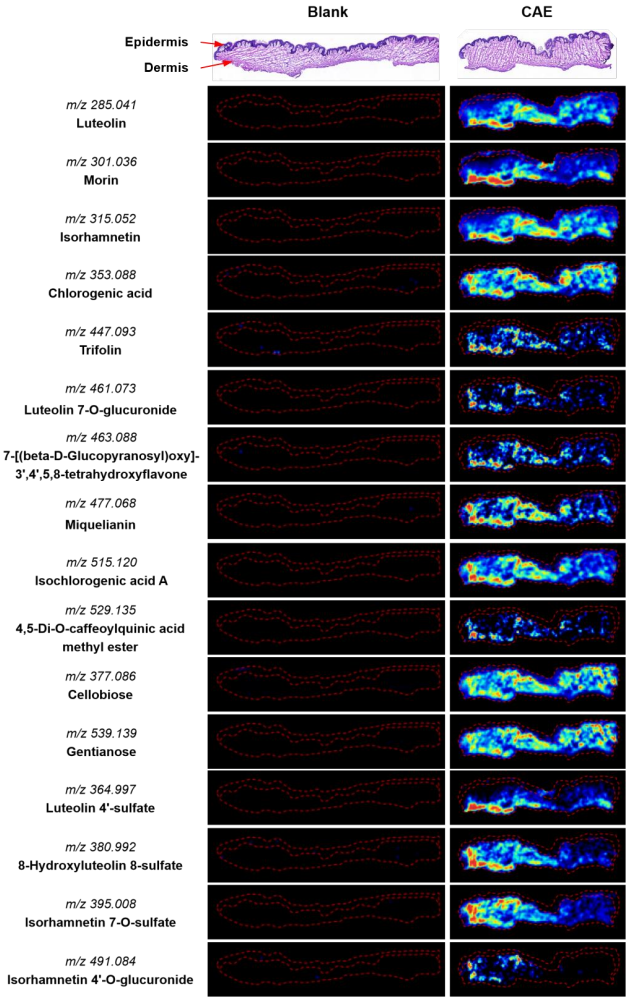

Figure 2. Mass Spectrometry Imaging Map of CAE Transdermal Absorption.

CAE soothing efficacy mechanism analysis based on multi-omics

To further clarify the efficacy mechanism of CAE, we conducted RNA-seq, proteomic, and metabolomic analyses on C48/80-induced RBL-2H3 cells. Multi-omics analysis revealed significant changes in multiple signaling pathways (such as the FoxO signaling pathway, cAMP signaling pathway, PI3K-Akt signaling pathway, and MAPK signaling pathway) and metabolic pathways (such as Arginine biosynthesis and Purine metabolism) across various omics levels. In the C48/80-induced cell model, inflammatory effector factors including Fos, Jun, Csf1, Lif, Ptgs1, Ptgs2, and pro-inflammatory factors (HETEs) were significantly upregulated. After CAE treatment, the expression of these related genes was inhibited in a dose-dependent manner (Fig. 3A-C). The expression of AMPK proteins (Prkaa1 and Prkag1) was upregulated in the CAE-treated group (Fig. 3B). Molecular docking results indicated that the transdermally absorbed components of CAE, Luteolin and Isochlorogenic acid A, could dock with the IL1R receptor; Luteolin, Trifolin, and Chlorogenic acid could dock with the IFNGR receptor; and Luteolin, Morin, Isorhamnetin, and Isochlorogenic acid A could dock with intracellular proteins PTGS1 and PTGS2 (Table 2). These components collectively regulate the AP-1-mediated inflammatory signaling pathway (Table 2, Fig. 3E). The results of metabolomics indicated that the level of the pro-inflammatory factor 8R-HETE decreased in CAE treatment group cells, while the contents of metabolites related to antioxidant and anti-inflammatory effects (such as Glutathione, Inosine, and Glyceric acid) significantly increased. These results were consistent with those from spatial metabolomics (Fig. 3C-D).

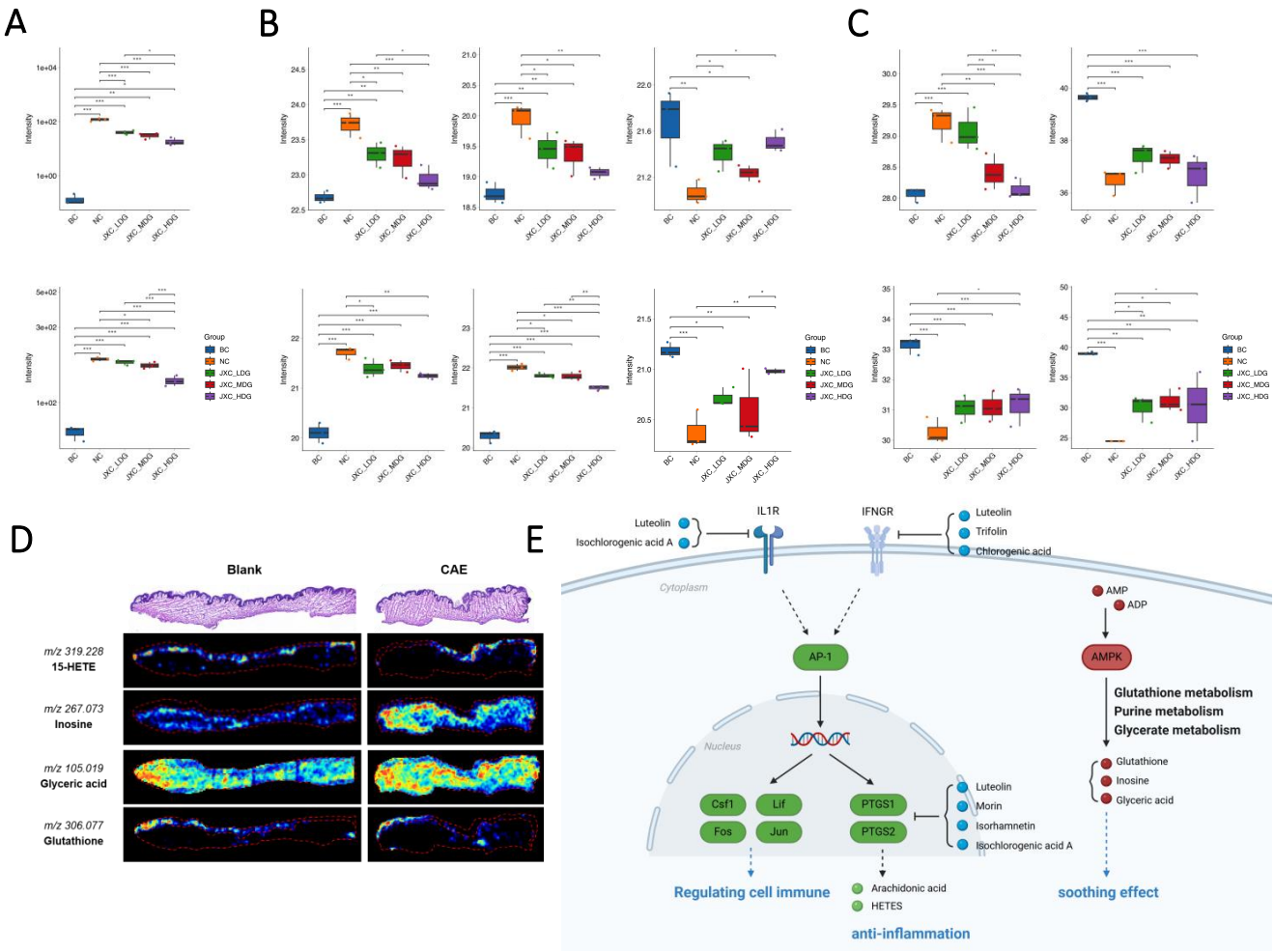

Figure 3. Multi-omics Analysis of CAE Soothing Efficacy Molecular Mechanism**.** A, Box plots of the content distribution of key genes across different groups; B, Box plots of the content distribution of key proteins across different groups; C, Box plots of the content distribution of key metabolites across different groups; D, Mass spectrometry imaging map of key metabolites; E, Molecular regulation diagram of CAE soothing effect of on C48/80-induced cellular inflammation.

Table 2. Molecular Docking

GeneName	UniProtID	MetaboliteName	Affinity (kcal/mol)
IL1R1	P14778	Luteolin 7-O-glucuronide	-9.223
IL1R1	P14778	Isochlorogenic acid A	-9.656
IFNGR1	P15260	Luteolin 4'-sulfate	-8.099
IFNGR1	P15260	Luteolin 7-sulfate	-8.211
IFNGR1	P15260	Luteolin 7-O-glucuronide	-9.054
IFNGR1	P15260	Trifolin	-8.127
IFNGR1	P15260	Chlorogenic acid	-9.372
CALM1	P0DP23	Isochlorogenic acid A	-9.232
SMAD3	P84022	Gentianose	-10.61
SMAD3	P84022	Chlorogenic acid	-9.285
PTGS1	P23219	Luteolin	-12.035
PTGS1	P23219	Luteolin 7-sulfate	-12.157
PTGS1	P23219	Luteolin 4'-sulfate	-13.406
PTGS1	P23219	Isorhamnetin	-10.199
PTGS1	P23219	Isochlorogenic acid A	-8.483
PTGS2	P35354	Luteolin	-11.97
PTGS2	P35354	Luteolin 4'-sulfate	-13.572
PTGS2	P35354	Morin	-12.11
PTGS2	P35354	Isorhamnetin	-12.63
PTGS2	P35354	Isochlorogenic acid A	-8.517
FGFR1	P11362	Asiatic acid	-9.137
FGFR1	P11362	Asiaticoside	-10.46
FGFR1	P11362	Isoasiaticoside	-12.078
FGFR1	P11362	Madecassic Acid	-8.23
FGFR1	P11362	Madecassoside	-12.009
FGFR1	P11362	Luteolin 4'-sulfate	-8.274
FGFR1	P11362	Luteolin 7-O-glucuronide	-10.228
FGFR1	P11362	Luteolin 7-sulfate	-9.312
FGFR1	P11362	Trifolin	-10.444
FGFR1	P11362	Isorhamnetin 4'-O-glucuronide	-9.297
PIK3R3	Q92569	Luteolin 7-O-glucuronide	-8.033
PIK3R3	Q92569	Trifolin	-11.508
PIK3R3	Q92569	Isorhamnetin 4'-O-glucuronide	-9.996

By integrating the findings from multi-omics, mass spectrometry imaging, and molecular docking, we depicted a molecular regulation pattern diagram (Fig. 3E) for the soothing efficacy of CAE: The active substances in CAE, including Luteolin, Chlorogenic acid, and Trifolin, as well as their metabolites, can competitively bind to IL1R and IFNGR, thereby regulating the function of their downstream transcription factor AP-1 and potentially inhibiting its translocation to the nucleus. This, in turn, affects the expression of a series of downstream key proteins (such as Csf1, Lif, PTGS1, and PTGS2), reducing the release of inflammatory factors. After CAE treatment, the increased levels of AMP and ADP activate the AMPK pathway, enhancing the synthesis and release of metabolites related to soothing efficacy, such as Glutathione, Inosine, and Glyceric acid. In addition, the four components in CAE, namely Luteolin, Morin, Isorhamnetin, and Isochlorogenic acid A, along with their metabolites, can directly interact with PTGS1/2 upon entering the cells, inhibiting the production of pro-inflammatory metabolites Arachidonic acid and HETEs, and collectively alleviating the local immune response of the cells to restore their growth and metabolic homeostasis.

Anti-wrinkle and firming soothing efficacy mechanism analysis based on multi-omics

By employing a multi-omics research strategy, we explored the mechanism of action of CAE in anti-wrinkle and firming effects on fibroblasts. The omics study results revealed that

CAE treatment could significantly increase the protein levels of COL1A1, COL3A1, and Fibronectin (FN1) in cells (Fig. 4B). Collagen synthesis is primarily regulated by growth factors such as TGF-β. Multi-omics data analysis indicated that several key genes/proteins (TGFB2, SMAD3, p21) in the TGF-β signaling pathway were activated by CAE treatment (Fig. 4A-B). p21 (CDKN1A) is a cyclin-dependent kinase inhibitor. When cells are damaged by external factors such as toxins or radiation, the activated p21 protein can inhibit cell division and initiate cell self-repair. CAE treatment suppressed the expression of cyclins downstream of p21, including CDK2 (CDK2), CycD (CCND1), CycE (CCNE2), and CycA (CCNA2). Meanwhile, the PI3K-AKT signaling pathway (PIK3R3), which negatively regulates p21, was also affected by CAE (Fig. 4A-B). The Calcium signaling pathway can regulate processes such as glycolipid metabolism and amino acid metabolism in cells [14]. After CAE treatment, the expression of CALM1 and CALML3 in the Calcium signaling pathway was enhanced (Fig. 4B), and metabolomics analysis revealed increased levels of L-Arginine, L-Tyrosine, and L-Phenylalanine downstream of the Calcium signaling pathway (Fig. 4C). Mass spectrometry imaging results showed similar trends in the changes of L-Arginine, L-Tyrosine, and L-Phenylalanine in ex vivo skin treated with CAE (Fig. 4D).

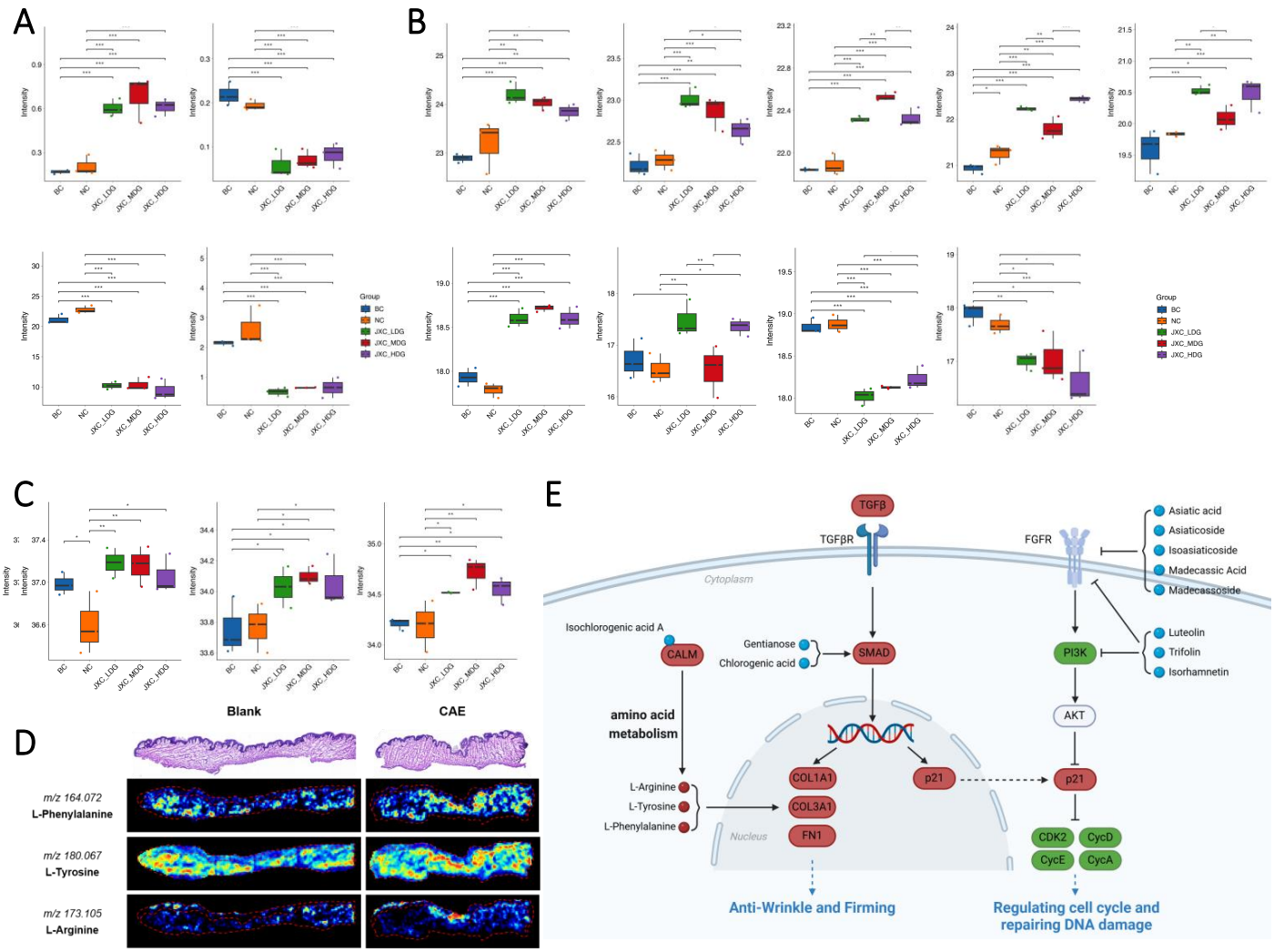

Figure 4. Multi-omics Analysis of CAE Anti-wrinkle and Firming Efficacy Molecular Mechanism. A, Box plots of the content distribution of key genes across different groups; B, Box plots of the content distribution of key proteins across different groups; C, Box plots of the content distribution of key metabolites across different groups; D, Mass spectrometry imaging map of key metabolites; E, Molecular regulation diagram related to CAE anti-wrinkle effect on UVA-irradiated human dermal fibroblasts.

By integrating the results from multi-omics, network pharmacology, and molecular docking (Table 2), we depicted a molecular regulation pattern diagram (Fig. 4E) for the anti-wrinkle and firming efficacy of CAE: CAE treatment upregulates the expression of TGFB2, activating the TGF-β Signaling pathway through TGFβR, which in turn activates the transcription factor SMAD3. Chlorogenic acid and Gentianose, the transdermal metabolic components of CAE, also bind to and activate SMAD3. Activated SMAD3 enters the nucleus and upregulates the expression of collagen proteins COL1A1 and COL3A1 and fibronectin FN1, exerting anti-wrinkle and firming effects. Additionally, SMAD3 can upregulate the expression of the cell cycle inhibitor p21. Important components of CAE, such as Asiaticoside, Isoasiaticoside, Madecassoside, Asiatic acid, and Madecassic Acid, can bind to the cell surface receptor FGFR. Transdermal components Trifolin, Luteolin, Isorhamnetin, and their metabolites can also competitively bind to the fibroblast growth factor receptor FGFR and PI3K (PIK3R3), collectively inhibiting the PI3K/AKT pathway and activating p21. Activated p21 can inhibit cell cycle regulatory proteins, regulate the cell cycle, and initiate DNA damage repair, collectively contributing to anti-wrinkle and firming effects. Isochlorogenic acid A, a transdermal component of CAE, also binds to CALM (CALM1 and CALML3), promoting the metabolism of L-Arginine, L-Tyrosine, and L-Phenylalanine through the Calcium signaling pathway, and participating in the synthesis of collagen and fibronectin.

Disscusion

Plant-based cosmeceuticals are gaining increasing recognition for their ability to promote skin health. Natural plant extracts are milder, more effective, safer, and free of side effects, making them highly suitable for skin needs and more environmentally friendly than traditional cosmetics [15]. *Centella asiatica* has been widely used in cosmetics due to its anti-inflammatory, antibacterial, antioxidant, and collagen-promoting properties. In this study, the soothing and anti-wrinkle/firming effects of CAE were confirmed through cellular experiments. Subsequently, we utilized LC-MS technology to elucidate the material basis of CAE's efficacy and combined network pharmacology to predict the potential targets and pathways of its active components.

Mass spectrometry imaging technology was employed for the first time to observe the transdermal absorption of multiple components of CAE in active ex vivo skin samples. Well-known active components in CAE, such as pentacyclic triterpenoids including asiaticoside, madecassoside, asiatic acid, and madecassic acid, were not found to be transdermally absorbed in this experiment, likely due to their relatively large molecular weights (greater than 500 Da). These compounds possess excellent anti-inflammatory and antibacterial activities and may exert their effects on the skin's outermost surface. Flavonoids and polyphenols (such as Luteolin, Morin, Isorhamnetin, etc.), with relatively smaller molecular weights, are more easily absorbed through the skin, reaching the epidermis and dermis, and thereby exerting soothing and anti-wrinkle/firming effects.

Activator Protein 1 (AP-1) is a critical transcription factor associated with numerous cellular functions, such as proliferation, apoptosis, cell migration, and transformation. AP-1 can be classified into five families: the JUN family, the FOS family, the Musculoaponeurotic fibrosarcoma (MAF) family, the Activating transcription factor (ATF) family, and the Jun-dimerizing partners [16]. Growing evidence suggests that AP-1 is involved in the regulation of inflammatory diseases, including inflammatory responses in the skin [17]. Additionally, many natural plant active ingredients have been reported to modulate inflammatory responses through AP-1, such as quercetin [18], Luteolin [19], isoquercitrin [20] and rutin [20]. In this study, it was found that transdermal absorption components of CAE, including Luteolin, Chlorogenic acid, Isochlorogenic acid A, Isorhamnetin, Trifolin, and their metabolites, can inhibit the AP-1 signaling pathway in RBL-2H3 cells, reducing the synthesis and release of inflammatory factors, and suppressing the expression and activity of PTGS1/2, thereby inhibiting the production of pro-inflammatory metabolites HETEs.

Overexposure to ultraviolet (UV) radiation leads to skin damage characterized by evident

signs of photoaging, such as wrinkle formation and skin roughness. UV radiation inhibits the TGF-β1/Smad pathway and reduces the expression of type I collagen [21]. Multiple studies have found that Centella asiatica extract and its active ingredients can enhance collagen synthesis and promote wound healing and skin repair by activating the TGF-β/Smad pathway in the skin [22]. In this study, we observed upregulated expression of the TGFB2 gene and SMAD3, COL1A1, and FN1 proteins in fibroblasts treated with CAE. These results are consistent with previous studies, indicating that CAE can achieve anti-wrinkle effects through the TGF-β/Smad signaling pathway.

The cyclin-dependent kinase inhibitor p21 (CDKN1A) is a well-known cell cycle inhibitor that can block cell cycle progression by inhibiting G1/S and G2/M transitions. When DNA damage occurs, p21 can induce cell cycle arrest, prompting cells to complete DNA damage repair, thereby maintaining genome stability and inhibiting tumor cell proliferation [23]. Previous studies have found that many natural plant products can trigger cell cycle arrest and inhibit the occurrence and growth of skin cancer by activating p21 function [24]. In this study, we found that CAE can activate p21, inhibit cell cycle progression, and repair UV radiation-induced cell damage through the TGF-β/Smad signaling pathway and the PI3K-AKT signaling pathway.

Skin aging is primarily associated with increased intracellular reactive oxygen species (ROS) levels and oxidative stress, elevated inflammation levels, and decreased collagen levels [25]. Metabolites such as amino acids, organic acids, and nucleotides have been confirmed to possess anti-skin-aging effects [26]. We found that the transdermally absorbed active components of CAE upregulated the levels of anti-aging-related metabolites such as Glutathione, Inosine, Glyceric acid, L-Arginine, L-Tyrosine, and L-Phenylalanine in the skin. Combined with multi-omics results, these changes in endogenous metabolites may be related to the upregulation of Ca signaling pathway and AMPK pathway induced by CAE.

Conclusions

Through a systematic research strategy that combines efficacy evaluation using cell models with ingredient analysis, network pharmacology, mass spectrometry imaging, and multi-omics detection, we found in this study that CAE possesses soothing, anti-wrinkle, and skin-tightening efficacy. Its main active ingredients, such as Luteolin, Morin, Isorhamnetin, Isochlorogenic acid A, Asiaticoside, and Asiatic acid, can exert soothing, anti-wrinkle, and skin-tightening effects by regulating AP-1-mediated inflammation-related signaling pathways, the AMPK Signaling pathway, the TGF-β/Smad signaling pathway, and the PI3K-AKT signaling pathway. These efficacy include inhibiting cellular inflammation, activating cellular collagen synthesis, and promoting the synthesis of anti-inflammatory and antioxidant metabolites.

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