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The antitumor effect of *Scutellaria barbata* D. Don (skullcap) aqueous extract and its mechanism of action in lung adenocarcinoma

[El efecto antitumoral del extracto acuoso de *Scutellaria barbata* D. Don (skullcap) y su mecanismo de acción en el adenocarcinoma pulmonar]

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Abstract: We aimed to explore the inhibitory effects of Scutellaria barbata D. Don (skullcap) aqueous extract (SBE) on the growth and migration of lung cancer cells and analyze underlying mechanism via bioinformatics analysis. SBE effectively inhibited the proliferation and migration of lung adenocarcinoma A549 cells assessed by experimental study. Wogonin is one of the active ingredients of SBE, and its target, CDK1, was selected by network pharmacology. CDK1 expression was greater in lung adenocarcinoma (LUAD) tissues than in normal tissues according to GEPIA2 and UALCAN and related to the progression and prognosis of LUAD. CDK1 expression was downregulated after SBE treatment in A549 cells. SBE inhibited the proliferation and migration of lung adenocarcinoma cells by regulating the expression of CDK1 and related genes involved in cell cycle regulation, progesterone-mediated oocyte maturation and the p53 signaling pathway. CDK1 might be an effective target of SBE and a potential prognostic biomarker in LUAD.

Keywords: *Scutellaria barbata* D. Don; Lung adenocarcinoma; Cell migration and invasion; CDK1; Bioinformatics

Resumen: Nuestro objetivo fue explorar los efectos inhibitorios del extracto acuoso de *Scutellaria barbata* D. Don (skullcap) (SBE) sobre el crecimiento y la migración de células de cáncer de pulmón y analizar el mecanismo subyacente a través de un análisis bioinformático. El SBE inhibió efectivamente la proliferación y migración de células de adenocarcinoma pulmonar A549, según lo evaluado en el estudio experimental. El wogonin es uno de los ingredientes activos del SBE, y su objetivo, CDK1, fue seleccionado mediante farmacología de redes. La expresión de CDK1 fue mayor en tejidos de adenocarcinoma pulmonar (LUAD) que en tejidos normales, de acuerdo con GEPIA2 y UALCAN, y se relacionó con la progresión y pronóstico de LUAD. La expresión de CDK1 se downreguló después del tratamiento con SBE en células A549. El SBE inhibió la proliferación y migración de células de adenocarcinoma pulmonar regulando la expresión de CDK1 y genes relacionados involucrados en la regulación del ciclo celular, la maduración del ovocito mediada por progesterona y la vía de señalización p53. CDK1 podría ser un objetivo efectivo del SBE y un potencial biomarcador pronóstico en LUAD.

Palabras clave: *Scutellaria barbata* D. Don; Adenocarcinoma pulmonar; Migración e invasión celular; CDK1; Bioinformática

INTRODUCTION

Lung cancer is the most common cancer; according to global cancer statistics reported by GLOBOCAN 2022, among cancers, the incidence and mortality of lung cancer worldwide are the highest at 12.4% and 18.7%, respectively (Bray *et al*., 2024). Currently, the three most common methods for treating lung cancer are surgery, chemotherapy, and radiotherapy (Singh *et al*., 2018). Although chemotherapy is the first-line treatment, the application of traditional chemotherapy drugs is limited due to toxicity and drug resistance (He *et al*., 2021). Therefore, the development of novel drugs with lower toxicity is urgently needed for lung cancer patients.

SB is a well-known herb of Labiatae and is widely distributed in southern China. Recent pharmacological investigations have confirmed that SB has antitumor, bacteriostatic, antiviral, antioxidative and anti-inflammatory properties (Chen *et al*., 2020). Previous studies have also shown that SB has an inhibitory effect on various tumors, including lung cancer, colorectal cancer, liver cancer, cervical cancer, leukemia, prostate cancer, breast cancer and ovarian cancer (Yu *et al*., 2017; Zhang *et al*., 2017; Ma *et al*., 2020; Xu *et al*., 2021; Liu *et al*., 2022; Sheng *et al*., 2022; Xue *et al*., 2022). Nevertheless, the effect of SB on metastasis in lung cancer and the underlying molecular mechanisms have not yet been elucidated.

In this study, we investigated the inhibitory effects of SBE on the proliferation and migration of lung adenocarcinoma A549 cells. Subsequently, we explored the underlying mechanism based on bioinformatics. We confirmed that CDK1 expression plays an important role in the progression and prognosis of lung adenocarcinoma. SBE might inhibit the growth and metastasis of lung cancer cells by downregulating the expression of CDK1. We found that CDK1 might be an effective target of SBE in lung adenocarcinoma.

MATERIALS AND METHODS

Regents and materials

Dulbecco's modified Eagle's medium (DMEM), penicillin/streptomycin solution and 0.25% trypsin-EDTA were purchased from Gibco BRL (Grand Island, NY, USA). Fetal bovine serum (FBS) was purchased from Gibco/Invitrogen (Auckland, New Zealand). SBE was obtained from China Resources Sanjiu Medical & Pharmaceutical Co., Ltd. (Hefei, Anhui Province, China) and dissolved in phosphate-buffered saline (PBS) before each experiment. DMSO was purchased from Beijing Solarbio Science & Technology Co., Ltd. (Beijing, China). Cell Counting Kit-8 (CCK8) was obtained from Beyotime Biotechnology (Shanghai, China). Transwell chambers were purchased from Corning Incorporated (Corning, NY, USA). Primary antibodies [anti-Matrix Metallopeptidase 2 (MMP-2), anti-Matrix Metallopeptidase 9 (MMP-9), anti-CDK1, and anti-GAPDH] were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA).

Cell culture

The lung cancer A549 cell line was obtained from the Henan Children's Hospital from Dr. Yuchun Liu. The cells were cultured in DMEM supplemented with 10% FBS, streptomycin (100 μg/mL) and penicillin (100 units/mL) at 37°C in 5% CO_2. Cells were digested with 0.25% trypsin-EDTA and treated with different concentrations of SBE.

CCK8 assay

A549 cells were seeded (2×10^3cells/well) in 96-well plates and incubated with media supplemented with different concentrations (0, 40, 80, 120, 240, or 360 μg/mL) of SBE for 24, 48, or 72 h. Cell viability was determined by adding 10 μL of CCK-8 reagent to each well. After incubation with CCK-8 reagent for 1h at 37°C, the optical density was measured at 450 nm.

Wound healing assay

Cell migration was assessed by a wound healing assay. A549 cells were seeded into 6-well cell culture plates at a density of 5×10^4 cells/mL and cultured until 100% confluence. Then, a scratch was made in the center of each well with a 200 μL pipette tip. The cells were washed twice with PBS to remove detached cells. Next, the cells were treated with different concentrations of SBE for 24 h, and the scratches were photographed and recorded in the same observation area. The wound healing area in each well was measured by the ImageJ program.

Transwell assay

Cell invasion was evaluated with a transwell chamber assay. Cells (1×10^4 cells) were seeded in a Matrigel-coated chamber with serum-free medium containing different concentrations of SBE. After 48 h of

incubation, the cells in the upper chamber were removed with cotton swabs. The invasive cells were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet. Then, the cells were photographed and counted in six random fields under a microscope.

Western blot analysis

Total protein was extracted from cells treated with different concentrations of SBE for 48 h. Protein concentrations were measured using a BCA Quantification Kit. Total protein samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to PVDF membranes. Then, the membranes were blocked in 5% fat-free milk for 1.5 h and incubated with primary antibodies overnight at 4°C. The next day, the membranes were washed with 1×TBST three times and incubated with secondary antibody for 2 h at room temperature. Then, protein bands were visualized using an enhanced chemiluminescence (ECL) kit.

Screening of active ingredients in and prediction of potential targets of SBE

The chemical compounds in SBE were investigated via the Traditional Chinese Medicines for Systems Pharmacology Database (TCMSP) (**http://lsp.nwu.edu.cn/tcmsp.php**) and Traditional Chinese Medicine Information Database (TCM-ID) (**https://www.bidd.group/TCMID/**). In TCMSP, oral bioavailability (OB ≥ 30%) and drug likeness (DL ≥ 0.18) were set as screening parameters to confirm the active compounds of SBE. Then, we acquired the common compounds from TCMSP and TCM-ID via the Venn diagram generation software Venny 2.1 (**https://bioinfogp.cnb.csic.es/tools/venny/index.html**). Simultaneously, the common compound-related targets were identified using TCMSP. The UniProt database (**https://www.uniprot.org**) was used to transform target proteins into corresponding genes. The PubChem database (**https://pubchem.ncbi.nlm.nih.gov**) was used to search for SMILES of common compounds, and the SMILES was imported into the Swiss Target Prediction (**http://www.swisstargetprediction.ch**) database to obtain the potential targets of the common chemical compounds. In the same way, we acquired the common potential targets from the TCMSP and Swiss Target Prediction databases via the Venn diagram generation software Venny 2.1.

Expression analysis of target genes and survival analysis of LUAD patients

We used Tumor Immune Estimation Resource (TIMER) (**https://cistrome.shinyapps.io/timer/**) and Gene Expression Profiling Interaction Analysis (GEPIA) (**http://gepia2.cancer-pku.cn/**) to analyze the expression of target genes in diverse cancers. The expression of target genes in LUAD was analyzed through GEPIA2 and University of Alabama at Birmingham Cancer (UALCAN) (**http://ualcan.path.uab.edu/**). The correlation between target genes and cancer pathological stage was explored by using the "stage plot" of GEPIA2 and UALCAN. Moreover, GEPIA2 and UALCAN were used to compare the associations between target gene expression and survival. The cutoff for differentiating between the high- and low-expression groups was 50%, and the "survival analysis" results were compared by the log-rank test.

Functional annotation analysis of protein–protein interaction (PPI) networks

STRING (**http://string-db.org**) was used to construct a PPI network of CDK1 with a minimum required interaction score of 0.4. In addition, GeneMANIA (**https://genemania.org**) was utilized to construct gene interaction networks of CDK1 and predict its functions. The correlation between CDK1 expression and related genes was predicted by TIMER 2.0. Metascape (**https://metascape.org**) was subsequently used for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of genes interacting with CDK1.

Statistical analysis

The data are expressed as mean values ± SDs. Statistical significance was determined using Student's t test or one-way ANOVA. All the statistical analyses were performed using GraphPad Prism Software. p values <.05 were regarded as statistically significant.

RESULTS

SBE inhibited A549 cell proliferation and migration

To investigate the effects of SBE on A549 cell growth, we assessed the proliferation of A549 cells by measuring cell viability after treatment with different concentrations of SBE (0, 40, 80, 120, 240,

or 360 µg/mL) for 24 h, 48 h or 72 h. A549 cell proliferation significantly decreased in a dose- and time-dependent manner (Figure No. 1A). Furthermore, wound healing and transwell assays were used to evaluate whether SBE affects the migration and invasion of A549 cells. SBE reduced cell migration and invasion in a dose-dependent manner (Figure No. 1B and Figure No. 1C). Finally, we assessed the effect of SBE on the protein expression of MMP-2 and MMP-9 in A549 cells by western blot analysis. The results showed that the expression of MMP-2 and MMP-9 significantly decreased after treatment with SBE (Figure No. 1D). Taken together, these results demonstrated that SBE can effectively inhibit the proliferation and migration of A549 cells.

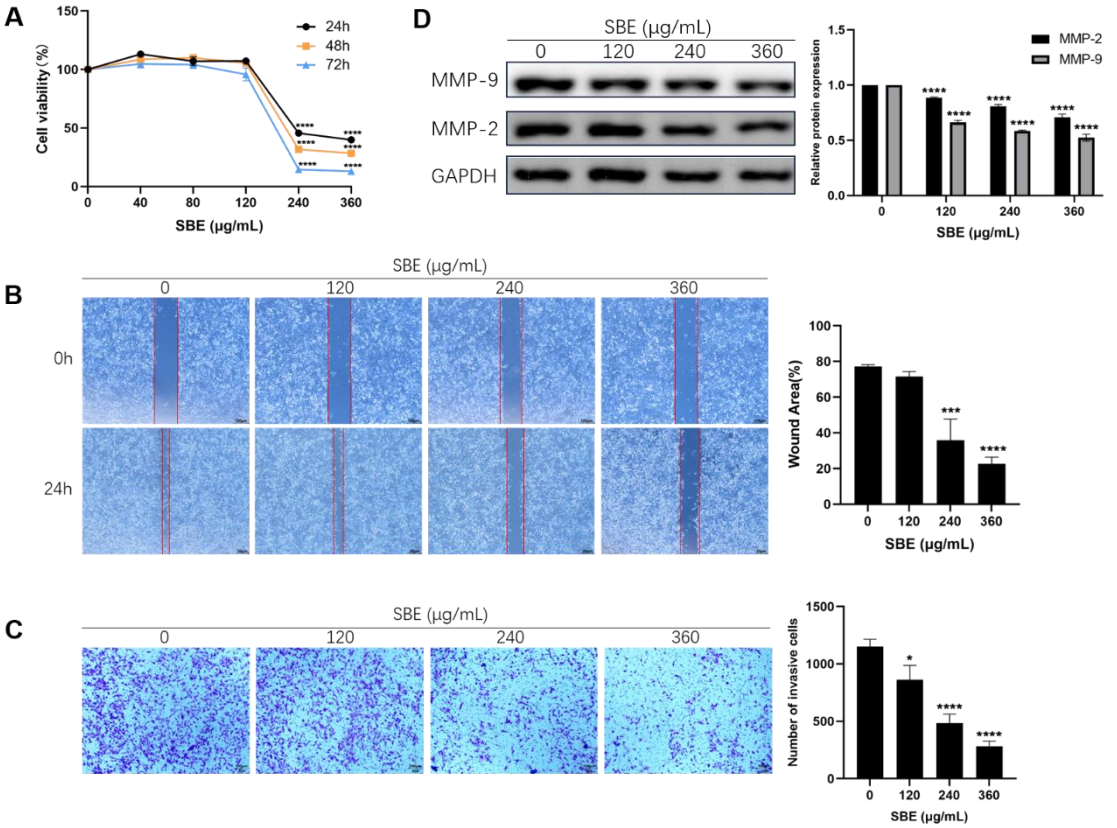
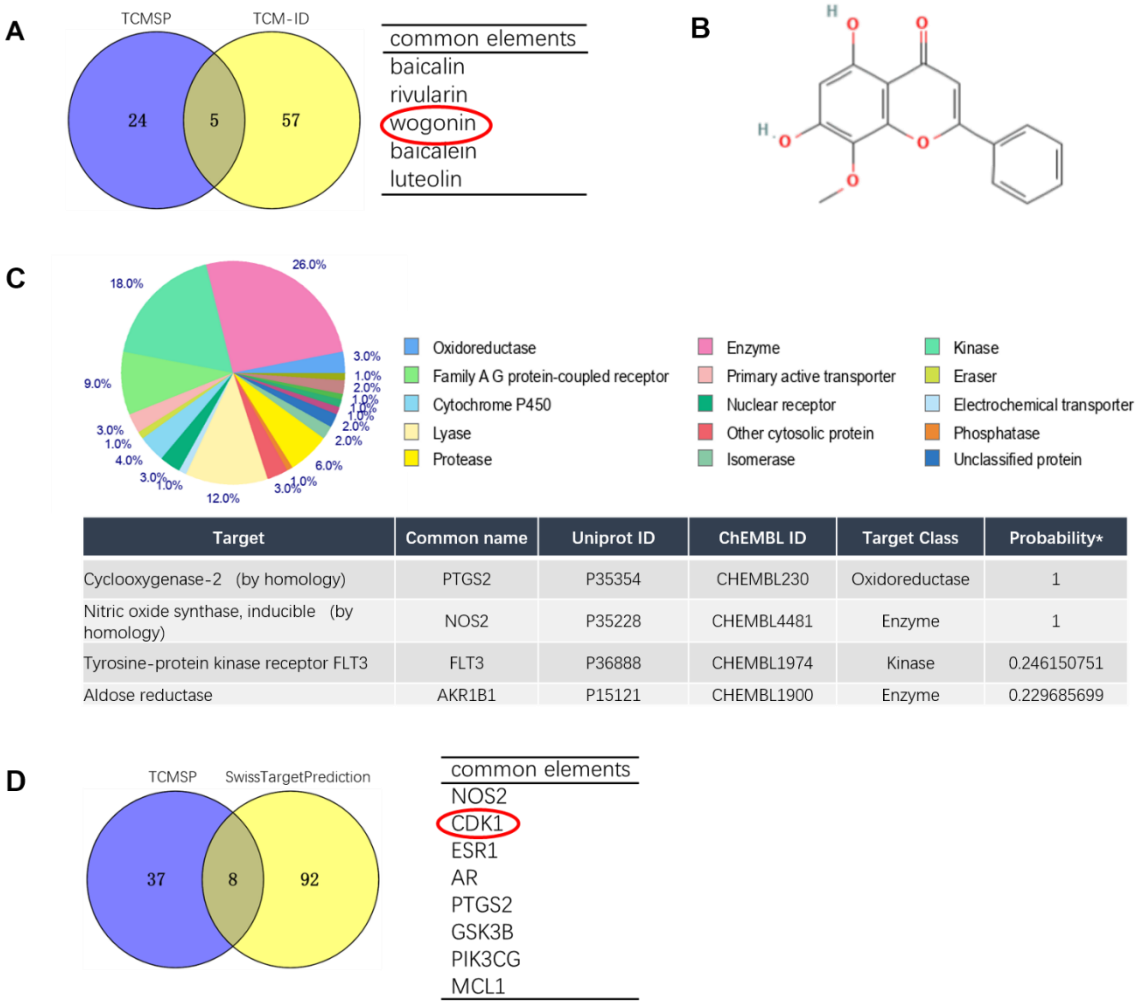


Figure No. 1

SBE inhibits A549 cell proliferation and migration. (A) A549 cells were treated with different concentrations (0, 40, 80, 120, 240, 360 µg/mL) of SBE for 24, 48, and 72h. A CCK8 assay was used to determine cell viability. (B) The cells were treatment with different concentrations (0, 120, 240, 360 µg/mL) of SBE for 24h, and then cell migration ability was assessed by a wound healing assay. (C) Effect of SBE on cell invasion was evaluated by a transwell chamber assay. (D) The expression levels of MMP-2 and MMP-9 was assessed through western blotting after treatment with various concentrations of SBE. All data were shown as means ± S.D. *p<0.05, **p<0.01, ***p<0.005 and ****p<0.0001 compared with the control group. SBE = *Scutellaria barbata* D. Don aqueous extract.

Active ingredients in and predicted targets of SBE

There were 29 active compounds of SBE identified from TCMSP. Concurrently, 62 active compounds were obtained from TCM-ID. Venn diagram analysis revealed 5 common compounds between the two datasets. Wogonin was included in the common compound subset (Figure No. 2A). The chemical structure of wogonin is shown in Figure No. 2B. Canonical SMILES of wogonin was searched in the PubChem database and imported into the Swiss Target Prediction platform. A total of 100 potential targets of wogonin were identified (Figure No. 2C). In the TCMSP, a total of 45 potential targets of wogonin were screened based on OB and DL. The two datasets were pooled for coanalysis, and 8 common targets were retrieved (Figure No. 2D). Furthermore, the CDK1 gene was included in the common target subset.

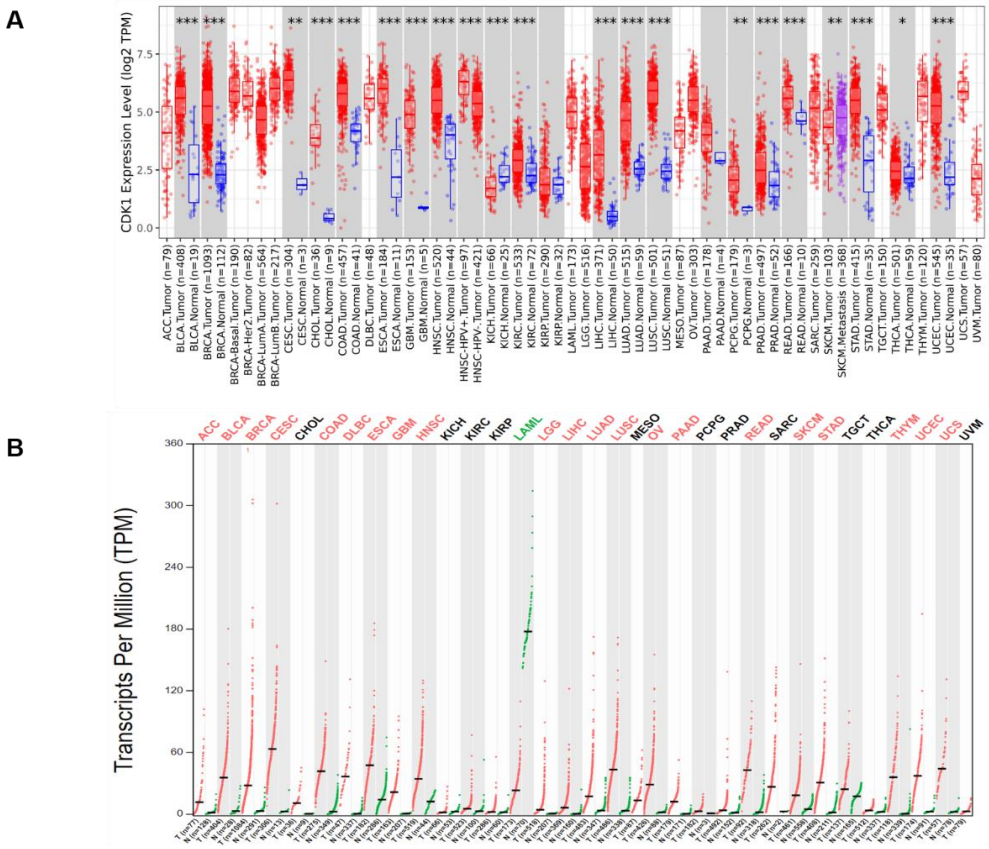


Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*
Cyclooxygenase-2 (by homology)	PTGS2	P35354	CHEMBL230	Oxidoreductase	1
Nitric oxide synthase, inducible (by homology)	NOS2	P35228	CHEMBL4481	Enzyme	1
Tyrosine-protein kinase receptor FLT3	FLT3	P36888	CHEMBL1974	Kinase	0.246150751
Aldose reductase	AKR1B1	P15121	CHEMBL1900	Enzyme	0.229685699

Figure No. 2
Active ingredients and target prediction of SBE. (A) Venn diagram of the active compounds of SBE. (B) Chemical Structure of Wogonin from TCMSP. (C) Targets database from SwissTargetPrediction using the Wogonin structure. (D) Venn diagram of the potential targets of Wogonin

Expression and prognostic role of CDK1 in LUAD

First, the expression of CDK1 in diverse cancers was explored with TIMER 2.0 and GEPIA2 (Figure No. 3A and No. 3B). Compared to the corresponding normal tissues, the majority of tumors, including bladder urothelial carcinoma (BLCA), cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), prostate adenocarcinoma (PRAD), and uterine corpus endometrial carcinoma (UCEC), exhibited increased expression of CDK1. Data from GEPIA2 and UALCAN demonstrated that CDK1 expression was significantly greater in LUAD tissues than in normal tissues (Figures No. 3C and No. 3D). Next, the associations between CDK1 expression and clinical parameters were analyzed. CDK1 expression was strongly correlated with tumor pathological stage (Figure No. 3E) and was significantly greater in the intermediate and advanced stages than in the earlier stages (Figure No. 3F). In terms of nodal metastasis status, CDK1 expression was significantly upregulated at the N0, N1, N2 and N3 stages compared to that in the normal group (Figure No. 3G). In addition, we explored the prognostic role of CDK1 in LUAD. Our data showed that CDK1 expression was correlated with OS and DFS in some tumors, such as kidney renal papillary cell carcinoma (KIRP), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), LUAD, and pancreatic adenocarcinoma (PAAD) (Figure No. 3H). Moreover, LUAD patients with higher expression of CDK1 had a significantly worse prognosis than patients with low expression of CDK1 according to the GEPIA and UALCAN datasets (Figures No. 3I, No. 3J and No. 3K). These findings indicated that CDK1 might play important roles in LUAD and has a potential function in tumor development and metastasis.



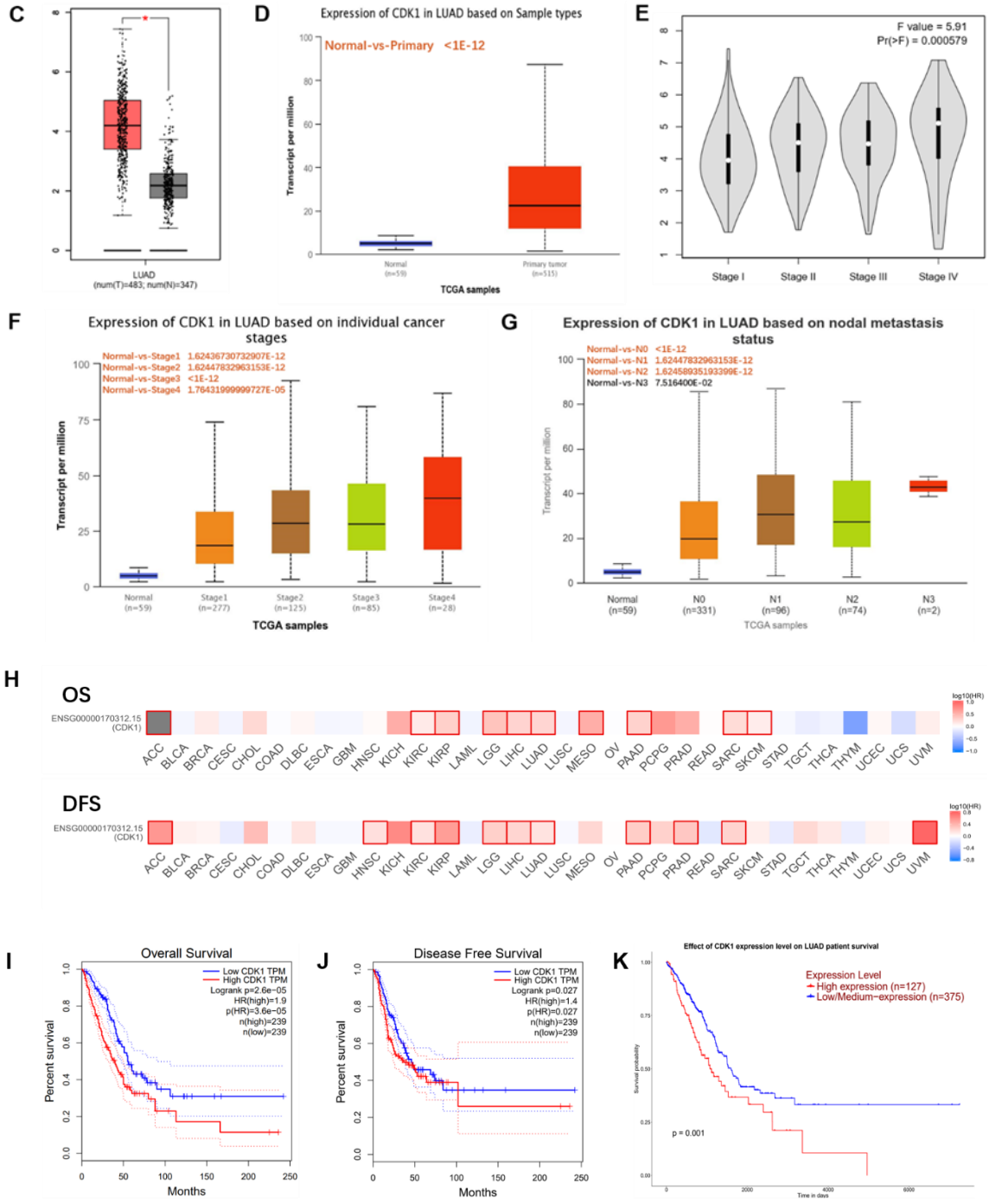
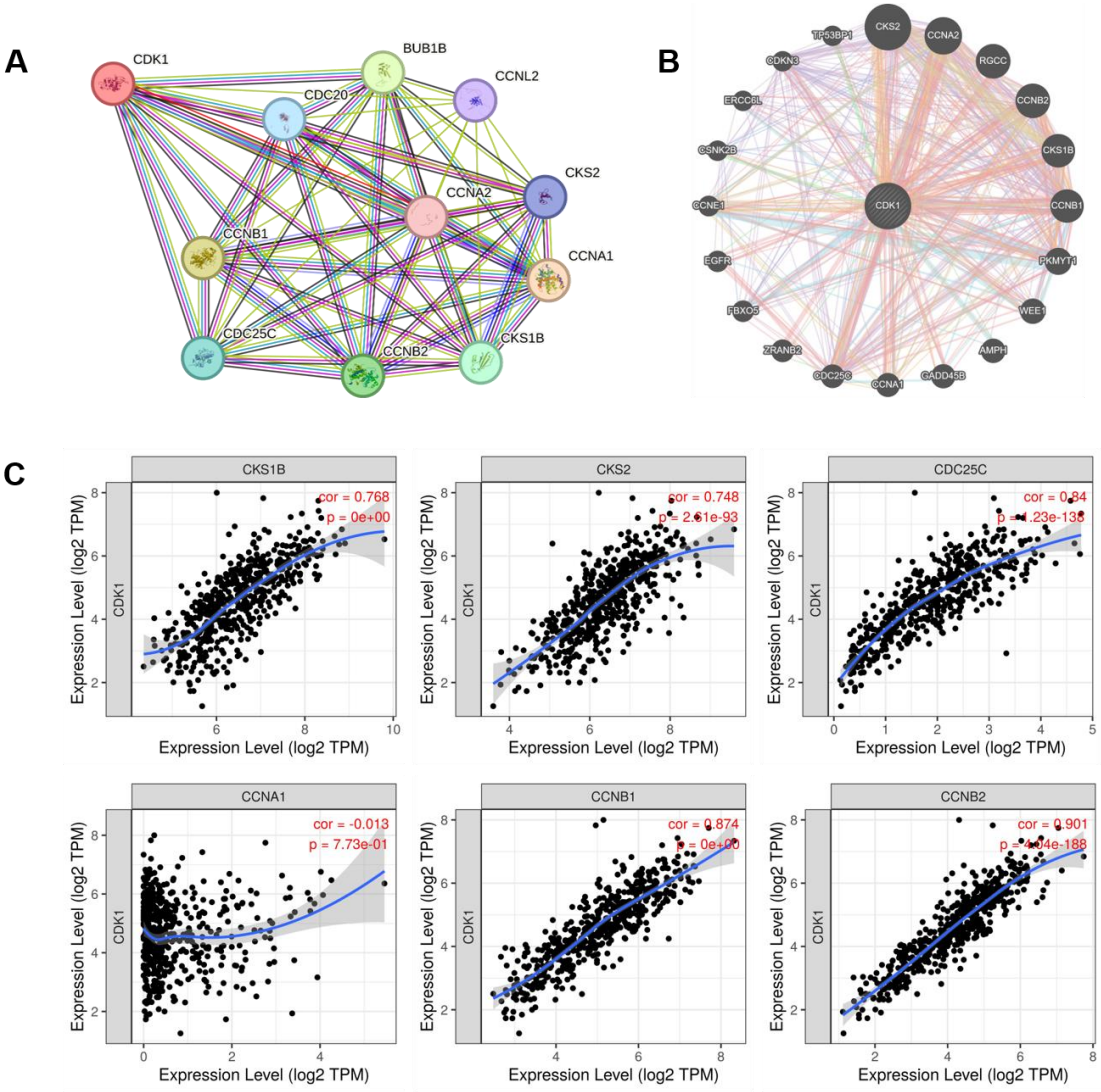


Figure No. 3

Expression and prognostic role of CDK1. (A-B) CDK1 expression in TIMER 2.0 database(A) and GEPIA2 database(B). (C-D) Expression of CDK1 gene in tumor and normal tissues in GEPIA2 (C) and UALCAN databases (D). (E–G) CDK1 expression in the different (E) pathological stages (I, II, III, and IV), (F) cancer stages (stage 1, 2, 3, 4), and (G) lymph node stages (N0 1, 2, and 3). (H) The correlation between CDK1 expression and OS and DFS across tumors through GEPIA 2 database. (I-K) The OS and DFS curves of LUAD with high and low CDK1 expression in GEPIA2 database (I-J) and UALCAN database (K). (*p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001)

PPI network and functional annotation

Ten genes correlated with CDK1 were obtained from the PPI network using the STRING database (Figure No. 4A). In addition, 20 candidate target genes associated with CDK1 were identified through GeneMANIA (Figure No. 4B). Analysis of the above datasets revealed six common members, namely, CKS1B, CKS2, CDC25C, CCNA1, CCNB1, and CCNB2. Moreover, TIMER 2.0 analysis revealed that all the common members except CCNA1 were significantly positively correlated with CDK1 expression in LUAD (Figure No. 4C). Finally, the five common genes from the PPI network were subjected to GO and KEGG pathway enrichment analyses. The GO analysis results showed that the genes were mainly enriched in biological processes, including mitotic cell cycle phase transition, cell cycle G2/M phase transition, regulation of the mitotic cell cycle, and nuclear division (Figure No. 4D). In addition, KEGG pathway analysis demonstrated that these genes were enriched in progesterone-mediated oocyte maturation and the p53 signaling pathway (Figure No. 4E).



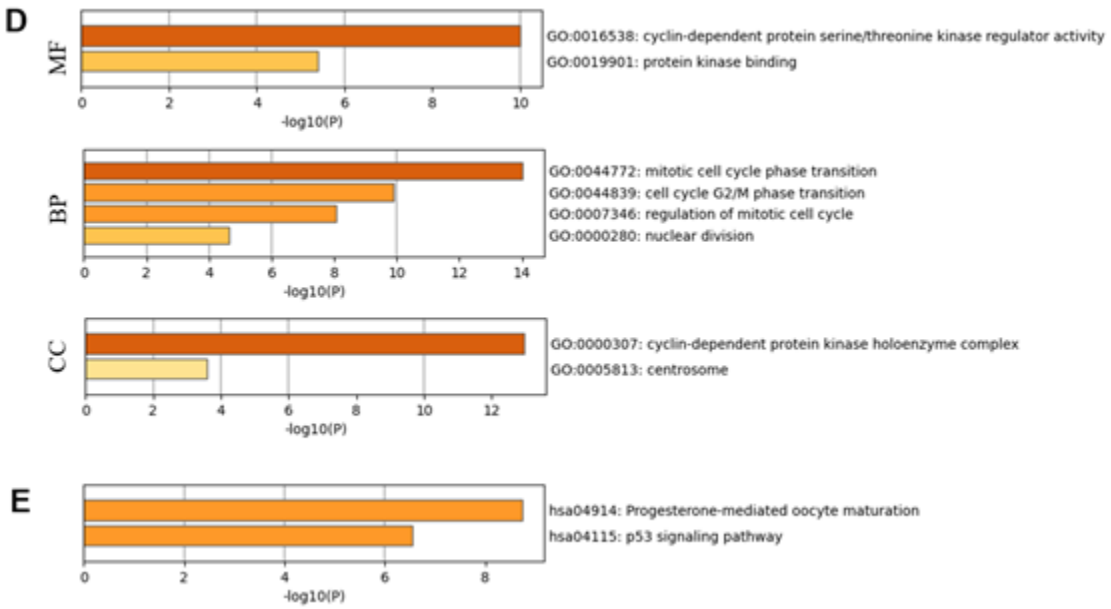


Figure No. 4
Enrichment analysis of CDK1 in LUAD. (A) CDK1-interaction proteins in LUAD obtained by STRING database. (B) The gene-gene network of CDK1 from GeneMANIA database. (C) Correlation between CDK1 expression and related genes in the TIMER 2.0 database. (D) GO enrichment analysis. (E) KEGG enrichment analysis. GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function, BP = biological process, CC = cellular component

SBE inhibited CDK1 expression in A549 cells

A549 cells were treated with different concentrations (0, 240, or 360 μg/mL) of SBE for 24h. The results showed that the expression of CDK1 was downregulated after SBE treatment in A549 cells (Figure No. 5).

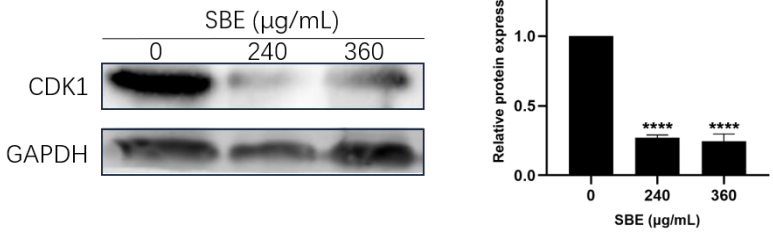


Figure No. 5
SBE inhibited the expression of CDK1 in A549 cells. A549 cells were treated with different concentrations (0, 240, 360 μg/mL) of SBE for 24h. Western blotting was used to evaluate the expression of CDK1

DISCUSSION

Lung cancer was the leading cause of cancer morbidity and mortality in 2022, with almost 2.5 million new cases and over 1.8 million deaths worldwide (Bray *et al*., 2024). Compared to current antitumor treatments, some natural compounds isolated from Chinese herbs have been proven to have antitumor effects with fewer side effects, such as polypeptides, gentiopicroside, ginsenoside compound K, worenine and so on (Ji *et al*., 2021; Chen *et al*., 2024; Jia *et al*., 2024; Liu *et al*., 2024). Traditional Chinese medicine (TCM) has been widely used to treat lung cancer due to its low toxicity (Liu *et al*., 2022b; Wei *et al*., 2023). SBE has positive effects on a variety of diseases, including various tumors. Our study revealed that the proliferation and migration ability of lung adenocarcinoma A549 cells were significantly inhibited by SBE. We further explored the active ingredients of SBE and their potential targets in lung cancer based on bioinformatics data analysis.

The analysis showed that there are numerous active ingredients in SBE, including baicalin, rivularin, wogonin, baicalein, and luteolin. Wogonin is a natural flavonoid compound that has been shown to have antitumor effects on lung cancer (Kimura & Suriyoshi, 2013; Zhao *et al*., 2018; Banik *et al*., 2022; Guo *et al*., 2023). Subsequently, the targets corresponding to wogonin were analyzed by network pharmacology. CDK1 is a potential target of wogonin. CDK1 plays an important role in the cell cycle and mitosis. Moreover, the association between CDK1 and various cancers has been studied. Several studies have shown that CDK1 plays an important role in the progression and treatment of breast cancer (Izadi *et al*., 2020). miR-495-3p and miR-143-3p inhibit the development of cervical cancer by targeting CDK1 (Tang *et al*., 2021). CDK1 inhibition has an effect on adaptive immune resistance in pancreatic cancer (Huang *et al*., 2021). Yang *et al*. (2016), reported that CDK1 is highly expressed in epithelial ovarian cancer cells and that knocking out CDK1 can induce apoptosis and cell death in ovarian cancer cells. Furthermore, we explored the role of CDK1 in lung cancer through a series of bioinformatics approaches.

CDK1 expression in LUAD and normal tissues was analyzed through the TIMER and GEPIA databases, and CDK1 expression was found to be higher in LUAD tissues than in normal tissues. In addition, upregulated CDK1 expression was significantly related to the occurrence and progression of LUAD. Furthermore, high CDK1 expression predicted a markedly worse prognosis in patients with LUAD. The above findings verified that CDK1 plays an important role in LUAD. CDK1 expression could effectively distinguish between tumor and normal samples and predict survival rates. These findings indicated that CDK1 is a potential biomarker for assisting in the diagnosis and prognosis of LUAD patients.

To further explore the molecular mechanism of CDK1 in LUAD, we searched for partner genes of CDK1 by PPI network and gene correlation analyses. The results showed that CDK1 was related to CKS1B, CKS2, CDC25C, CCNB1, and CCNB2. Subsequently, these genes were subjected to enrichment analysis, which showed that the functional mechanisms mainly involved cell cycle regulation, progesterone-mediated oocyte maturation and the p53 signaling pathway. Previous studies have shown that the cell cycle and progesterone-mediated oocyte maturation are activated pathways in LUAD (Yu *et al*., 2020; Tu *et al*., 2023). The p53 signaling pathway plays a very important role in pathological processes in LUAD (George *et al*., 2015; Zhang *et al*., 2023; Wei *et al*., 2024). Based on the above results, we believe that CKS1B, CKS2, CDC25C, CCNB1, CCNB2, and CDK1 are correlated with the pathogenesis and progression of LUAD. These genes might be involved in antitumor processes through the above signaling pathways. To further validate CDK1 as a target of SBE in LUAD, we assessed CDK1 expression after SBE treatment in A549 cells. The results showed that CDK1 expression was downregulated and that CDK1 was one of the targets of SBE in LUAD. Nonetheless, with our study partially based on bioinformatics analysis, experimental validation is necessary in future studies.

CONCLUSION

We explored the antitumor effect of SBE and analyzed the underlying mechanism in lung adenocarcinoma via bioinformatics analysis. In this study, SBE significantly inhibited the proliferation and migration of lung adenocarcinoma cells through regulating the expression of CDK1 and related genes involved in cell cycle regulation, progesterone-mediated oocyte maturation and the p53 signaling pathway. CDK1 might be an effective target of SBE

and a potential prognostic biomarker in LUAD.

ABBREVIATION

SB: *Scutellaria barbata* D. Don; SBE: *Scutellaria barbata* D. Don aqueous extract; CDK1: Cyclin-dependent kinase 1; LUAD: Lung adenocarcinoma; TCMSP: the Traditional Chinese Medicines for Systems Pharmacology Database; TCM-ID: Traditional Chinese Medicine Information Database; TIMER: the Tumor Immune Estimation Resource; GEPIA: Gene Expression Profiling Interaction Analysis; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; TCM: Traditional Chinese medicine.

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