Cancer Management and Research

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ORIGINAL RESEARCH

Baicalein Inhibits Proliferation, Migration, and Invasion of Mesothelioma Cells Through the p53–FOXM1 Signaling Axis

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Purpose: Baicalein, a natural flavonoid derived from the root of *Scutellaria baicalensis*, has demonstrated antitumor efficacy in several cancers. However, its effects on human mesothelioma remain largely unclear. This study evaluates the antitumor roles and mechanisms of baicalein in mesothelioma cell lines.

Materials and Methods: Effects of baicalein on mesothelioma cells phenotypic changes were investigated by measuring cell proliferation, apoptosis, migration, invasion, and cell-cycle alterations. Bioinformatic methods were applied to predict the mechanisms by which baicalien mediated its antitumor roles in mesothelioma. Crucial signaling molecules among p53-FOXM1 signaling axis, including p53, FOXM1 and cyclin B1, were evaluated by immunoblotting in mesothelioma cells.

Results: Treatment with baicalein significantly inhibited mesothelioma cell viability in a dose-dependent manner, with 48 h IC_{50} values of 48.9 μM for MESO257 and 53.2 μM for MESO924. Baicalein also markedly reduced cell migration and invasion, while inducing apoptosis in both cell lines. Mechanistically, baicalein suppressed the p53-FOXM1 signaling axis, decreasing FOXM1 and Cyclin B1 while increasing p53 expression. Furthermore, FOXM1 overexpression attenuated the antiproliferative, anti-migratory, anti-invasive and proapoptotic effects of baicalein.

Conclusion: Baicalein suppresses mesothelioma cell growth and invasion in vitro through modulation of the p53–FOXM1 signaling axis. These findings support its potential as a lead compound for further preclinical evaluation in mesothelioma.

Keywords: Baicalein, traditional Chinese medicine, antitumor activity, mesothelioma, p53, FOXM1

Introduction

Malignant mesothelioma (MESO) is a highly aggressive cancer primarily linked to significant asbestos exposure or SV40 infection.[1,2] It is categorized into three histological types: epithelioid, sarcomatoid, and biphasic (mixed) variants. Notably, the spindle cell variant, which predominantly arises from the sarcomatoid type, is associated with the worst prognosis.[3] Conventional treatments, including chemotherapy and radiotherapy, often prove ineffective, highlighting the urgent need for innovative therapies that offer lower toxicity and enhanced efficacy for mesothelioma patients.

Traditional Chinese medicine has gained recognition as a promising source of antitumor agents, demonstrating significant efficacy in cancer treatments over recent decades.[4] Flavonoids, widely utilized in Chinese herbal medicine, have been linked to a reduced risk of certain cancers in epidemiological studies. Baicalein, a key bioactive flavonoid derived from the root of *Scutellaria baicalensis* Georgi, exemplifies this potential,[5] Increasing evidence highlights baicalein's effectiveness in both treating and preventing various cancers.[6] Its anticancer properties primarily arise from its ability to inhibit inflammation and cell proliferation.[7,8] Additionally, baicalein's effects are mediated through the modulation of multiple cell-signaling pathways, including the induction of apoptosis, autophagy, and cell cycle arrest, as well as the inhibition of angiogenesis. It also influences key pathways such as the signal transducer and activator of transcription 3 (STAT3) and PI3K/Akt, along with other molecular targets.[9–13]

Received: 5 August 2025
Accepted: 9 December 2025
Published: 19 December 2025

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In mesothelioma, dysregulation of multiple oncogenic signaling pathways drives tumor progression and contributes to therapeutic resistance. Among these, FOXM1, a transcription factor that governs cell-cycle progression, DNA repair, and metastasis, is frequently overexpressed in mesothelioma and strongly associated with poor patient prognosis.[14,15] The tumor suppressor p53 has been shown to negatively regulate FOXM1 expression, indicating that disruption of the p53–FOXM1 signaling axis may represent a critical event in mesothelioma pathogenesis.[16] Baicalein, a natural flavonoid known to activate p53-related pathways and suppress oncogenic transcription factors in other cancers, may therefore exert antitumor effects in mesothelioma through modulation of this axis. However, this potential mechanism has not yet been explored.

The present study aimed to evaluate the effects of baicalein on the proliferation, apoptosis, migration, and invasion of mesothelioma cells, and to elucidate whether its anticancer activity involves regulation of the p53-FOXM1 signaling pathway. Our findings suggest that baicalein suppresses mesothelioma progression via this axis, supporting its potential as a promising therapeutic agent for patients with mesothelioma.

Materials and Methods

Antibodies and Reagents

Monoclonal mouse antibodies to p53 (Santa Cruz Biotechnology Cat# sc-126, RRID: AB_628082), cyclin B1 (Santa Cruz Biotechnology Cat# sc-245, RRID: AB_627338), and β-Actin (Santa Cruz Biotechnology Cat# sc-47778, RRID: AB_626632) were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Monoclonal rabbit antibodies to FOXM1 (#14655) were obtained from Cell Signaling Technology (Pudong, Shanghai, China). FOXM1 expression plasmid was purchased from Genecopoeia company (Guangzhou, Guangdong, China). DMSO (dimethyl sulfoxide) was obtained from Beijing Solarbio Science and Technology (Beijing, China). Baicalein was purchased from were from Sigma-Aldrich (St, Louis, MO) and was reconstituted in DMSO. The qRT-PCR primers of FOXM1 and GAPDH were synthesized by BiOligo Biotechnology (Shanghai, China).

Cancer Cell Lines

All studies involving the MESO257 and MESO924 cell lines were conducted under protocols approved by the Brigham and Women's Hospital Institutional Review Board (IRB). These cell lines were established from discarded surgical specimens obtained during routine clinical procedures from treatment-naïve patients with histologically confirmed epithelial-type malignant mesothelioma.The procurement and experimental use of these specimens were formally designated as exempt research under US Federal Regulation 45 CFR 46.104(d)(4) (Categories of Exempt Human Subjects Research). The Brigham and Women's Hospital IRB explicitly granted waiver of informed consent under their institutional Discarded Tissues Protocol, which governs the use of anonymized residual biological materials collected during standard-of-care interventions.Cell line authentication was performed through short tandem repeat (STR) profiling as previously published, with supplementary verification via persistence of tumor-specific cytogenetic aberrations.[14,15] Both cell lines were kindly provided by Dr. Wen-Bin Ou (College of Life Sciences, Zhejiang Sci-Tech University) and maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin at 37°C in 5% CO_2.

Cell Proliferation and Apoptosis Assays

MESO257 and MESO924 cells were cultured in 96-well plates at a density of 5×10^3 cells per well and incubated for 12 hours in RPMI-1640 basic medium. Different concentrations of baicalein or an equal volume of DMSO (vehicle control) were then added. After 48 hours of treatment, cell proliferation was evaluated using the Cell Proliferation Assay Kit (Promega, USA) according to the manufacturer's instructions. Cell viability data were analyzed using nonlinear regression (log[inhibitor] vs normalized response) in GraphPad Prism 8.0 to determine IC_{50} values. Results are expressed as mean ± SEM from three independent experiments (n = 3). The absorbance of each well was measured at 490 nm using a microplate reader. The relative cell viability was calculated after background subtraction (cell-free blank), and normalized to the DMSO control, which was set as 100% viability. The formula used was: Relative Cell Viability (Fold of Control) = $(OD_{Baicalein} - OD_{Blank}) / (OD_{DMSO} - OD_{Blank})$.

For apoptosis assays, MESO257 and MESO924 cells (5×10^3 cells/well) were seeded in 96-well plates and treated with various concentrations of baicalein or DMSO for 48 hours. Caspase-3/7 activity was measured using the Caspase-Glo® 3/7 Assay Kit (Promega, USA) following the manufacturer's protocol. Luminescence was detected using a microplate reader, and relative apoptosis was calculated as: Relative Cell Apoptosis (Fold of Control) = $(RLU_{Treatment} - RLU_{Blank}) / (RLU_{DMSO} - RLU_{Blank})$.

All experiments were performed in at least triplicate.

Cell Cycle Analysis

MESO257 and MESO924 cells cultured in six-well plates (1.2×10^6 cells/well) were trypsinized and washed once with Hank's balanced salt solution at room temperature following baicalein treatment for 48 h. For nuclear staining, a propidium iodide-containing solution (nuclear isolation and staining solution; NPE Systems, Pembroke Pines, FL, USA) was added to the cells, and the cell suspension was immediately analyzed using a BD Accuri™ C6 Plus Flow Cytometer (BD Biosciences, USA). Data analysis was performed with Modfit LT software 3.1 (Verity Software House, Topsham, ME, USA). Experiments were performed in triplicate.

In vitro Wound Healing Assay

The wound-healing assay was performed as previously described, with some modifications.[16] Briefly, MESO257 and MESO924 cells were plated in 6-well plates at a density of 1.2×10^6 cells per well for 12 hours. Once the cell density reached approximately 90–95% confluence, scratches were created in the wells using a 10 μL pipette. To minimize the potential influence of cell proliferation on wound closure, the cells were then cultured in 1640 containing 1% fetal bovine serum (FBS) with baicalein or DMSO treatment. After 12 hours of culture, the plates were photographed with a Nikon Elipse Ti2 microscope (Nikon, Tokyo, Japan) when the wound in the control group (DMSO treatment) was nearly healed. The wound area was quantified using ImageJ software, and the relative wound closure was calculated using the formula: Relative Wound Closure (Fold of Control) = $[(S_{0h} - S_{12h}) / S_{0h}]_{Baicalein} / [(S_{0h} - S_{12h}) / S_{0h}]_{DMSO}$. Experiments were performed in triplicate.

Matrigel Invasion Assays

Cell invasion was assessed using matrigel invasion assays with a transwell chamber system, as previously described with some modifications.[17] Briefly, the transwell inserts were coated with matrigel, and 5000 cells resuspended in 1640 basic medium containing 1% FBS and baicalein were seeded in the upper chamber. The lower chamber was filled with 15% FBS in 1640 basic medium to create a chemotactic gradient for cancer cell migration. After 48 hours of treatment, the cells in the upper chamber were gently removed with a cotton swab. The inserts were then fixed with 4% formaldehyde for 15 minutes and stained with 1% crystal violet for 10 minutes. Excess dye was washed away with phosphate-buffered saline, and crystal violet was eluted with 33% glacial acid and the OD was measured at 590 nm with an EnSight™ Multimode plate reader (Perkin Elmer, MA, USA) to quantify the invasive cells. Experiments were performed in triplicate.

RNA Isolation, qRT-PCR, and Transcriptome Sequencing

For the qRT-PCR assay, RNA extraction from cells was performed using a TIANGEN RNA extraction kit (DP430). cDNA synthesis was conducted with an M-MLV (Moloney murine leukemia virus) system (Promega, M1705), utilizing a 1 μg portion of total RNA, and the resulting complementary DNA was subjected to qPCR. For RNA sequencing, library construction and sequencing were carried out by Shanghai Majorbio Bio-pharm Biotechnology Co., Ltd. (Shanghai, China) following the manufacturer's instructions (Illumina, San Diego, CA). The primers for qRT-PCR were as follows: FOXM1 forward, 5'-CGTGGATTGAGGACCACTTT-3', and FOXM1 reverse, 5'-GGCTTAAACACCTGGTCCAA-3'; GAPDH forward, 5'-GGCCTCCAAGGAGTAAGACC-3', and GAPDH reverse, 5'-AGGGGTCTACATGGCAACTG-3'.

Experiments were performed in triplicate.

Gene Set Enrichment Analysis (GSEA)

The hallmark gene set (h.all.v7.1.symbols.gmt), consisting of 50 hallmark gene sets, was downloaded from MSigDB (https://www.gsea-msigdb.org/gsea/index.jsp). GSEA for Hallmark gene sets analysis and KEGG analysis were

performed by the R package "clusterProfiler", and the obtained gene sets were visualized in the form of bubble plots by the R package "ggplot2".[18,19] Bioinformatic analyses (including Gene Set Enrichment Analysis, KEGG pathway analysis, and GPSAdb correlation studies) were performed using publicly available databases. Gene sets with a $p < 0.05$ were regarded as statistically significant.

Western Blotting Analysis

Whole-cell lysates were prepared using lysis buffer composed of 1% NP-40, 50 mM Tris–HCl (pH=8.0), 100 mM sodium fluoride, 30 mM sodium pyrophosphate, 2 mM sodium molybdate, 5 mM EDTA, and 2 mM sodium orthovanadate, along with protease inhibitors (10 μg/mL aprotinin, 10 μg/mL leupeptin, and 1 mM phenylmethylsulfonyl fluoride). Lysates were cleared by centrifugation at 12,000 rpm for 30 min at 4°C, and the protein concentrations of the lysates were determined using a Bio-Rad protein assay (Bio-Rad Laboratories, Hercules, CA, USA). Electrophoresis and Western blotting assays were performed as previously described.[20] The hybridization signals were detected by ECL reagent (Millipore, USA) and captured using the Amersham ImageQuant™ 800 Western blot imaging systems (Cytiva, USA). Experiments were performed in duplicate.

Transfection

Transfection of FOXM1 expression vectors or the empty vectors into MESO257 and MESO924 cells was performed following Invitrogen's protocol using Lipofectamine and PLUS reagent. Briefly, DNA was incubated with PLUS reagent in 100 μL of serum-free medium for 15 min at room temperature. Lipofectamine was diluted in 100 μL of serum-free medium and added to the DNA-PLUS complexes, which were then incubated for an additional 15 min at room temperature. Subsequently, the DNA-PLUS-Lipofectamine complexes were added to cultures of MESO257 and MESO924 cells at about 80% confluence in 800 μL of serum-free medium in six-well plates, and the medium was completely replaced with serum-containing regular media after 6 h. Cells were lysed for Western blotting analysis at 48 after transfection.

Statistical Analysis

Data were analyzed using one-way ANOVA followed by Tukey's post hoc test in GraphPad Prism 8.0.1. Significant differences were defined as $*P < 0.05$, $** P < 0.01$ and $*** P < 0.001$.

Results

Baicalein Regulation of Mesothelioma Proliferation and Apoptosis

Given the antitumor effects of baicalein in various human cancers, but not in mesothelioma, we investigated its roles and mechanisms in mesothelioma cell lines (MESO257 and MESO924). First, we assessed the effect of baicalein on cell proliferation using a cell viability assay. Dose-response analysis showed that baicalein inhibited cell viability in a concentration-dependent manner. The 48 h IC_{50} values were 48.9 μM for MESO257 and 53.2 μM for MESO924 (Figure 1A). Consistent with this dose-response relationship, treatment with 50 μM and 100 μM baicalein significantly reduced the viability of both cell lines (Figure 1B).

Next, we analyzed cell cycle changes through flow cytometric DNA analysis to determine whether baicalein mediates cell cycle arrest to suppress mesothelioma cell proliferation. In MESO257 and MESO924, baicalein treatment led to a notable increase in the G2 peak and a slight decrease in the G1/S peak (Figure 1C). Together, these findings suggest that the inhibition of mesothelioma cell proliferation by baicalein may be attributed to cell cycle arrest in G2 phase.

We then performed a functional caspase 3/7 activation assay to evaluate whether baicalein regulates apoptosis in mesothelioma cells. The results indicated that baicalein treatment significantly increased caspase 3/7 activity in both MESO257 and MESO924 compared to the control group (DMSO treatment) (Figure 1D). These findings confirm that baicalein exhibits pro-apoptotic effects in mesothelioma cells.

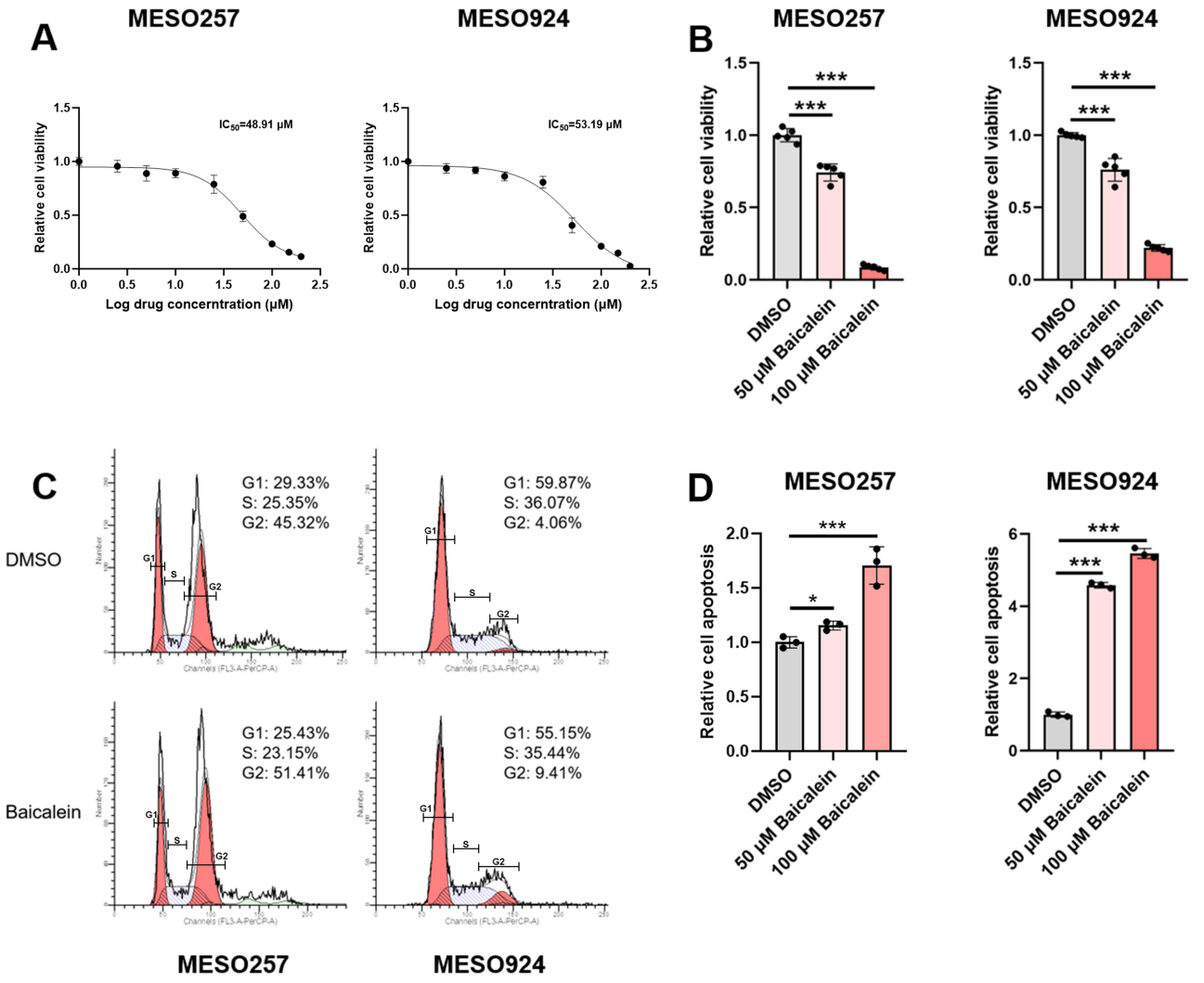

Figure 1 Cell viability, cell cycle, and cell apoptosis assessment for mesothelioma cells after baicalein treatment. (**A**) Dose-response curves of MESO257 and MESO924 cells after 48 h of baicalein treatment, showing concentration-dependent inhibition of cell viability. Data are normalized to DMSO control and shown as mean (±SEM; n = 3). (**B**) Cell viability assay was performed in MESO257 and MESO924 after incubation with baicalein for 48 h. Data are normalized to DMSO control and shown as mean (±SD; n = 5). Significant differences were defined as ***P< 0.001. (**C**) Cell-cycle analysis was performed after baicalein treatment for 48 h in MESO257 and MESO924. MESO257 and MESO924 cells show substantial G2-block after baicalein treatment when compared to DMSO. (**D**) Apoptosis was assessed in MESO257 and MESO924, at day 2 after incubation with baicalein. The activity of Caspase 3/7 was obtained with Caspase-Glo® luminescence assay. The data were normalized to the DMSO treatment and shown as mean (± SD; n = 3) and significant differences were defined as *P< 0.05 and ***P< 0.001.

Baicalein Regulation of Mesothelioma the Migration and Invasiveness

Metastatic mesothelioma is characterized by invasive growth and extension around the pleurae, heart (pericardium), and peritoneum. To evaluate the effects of baicalein on mesothelioma cell migration, we conducted wound-healing assays. The wound-healing assays for MESO257 and MESO924 revealed that baicalein treatment significantly inhibited wound closure compared to the control cells incubated with DMSO (Figure 2A).

Additionally, we performed transwell matrigel assays to assess the effect of baicalein on the invasion of mesothelioma cells. The results indicated that baicalein treatment markedly reduced the invasive capability of both MESO257 and MESO924 cells compared to the DMSO control group (Figure 2B). These findings suggest that baicalein effectively suppresses the metastasis and invasion of mesothelioma cells, highlighting its potential as a therapeutic option for patients with metastatic mesothelioma.

Baicalein Regulates the p53-FOXM1 Signaling Axis in Mesothelioma

Gene set enrichment analysis (GSEA) is a bioinformatics method used to determine whether predefined gene sets exhibit differential expression across different phenotypes.[21] Hallmark gene sets summarize specific biological states or processes

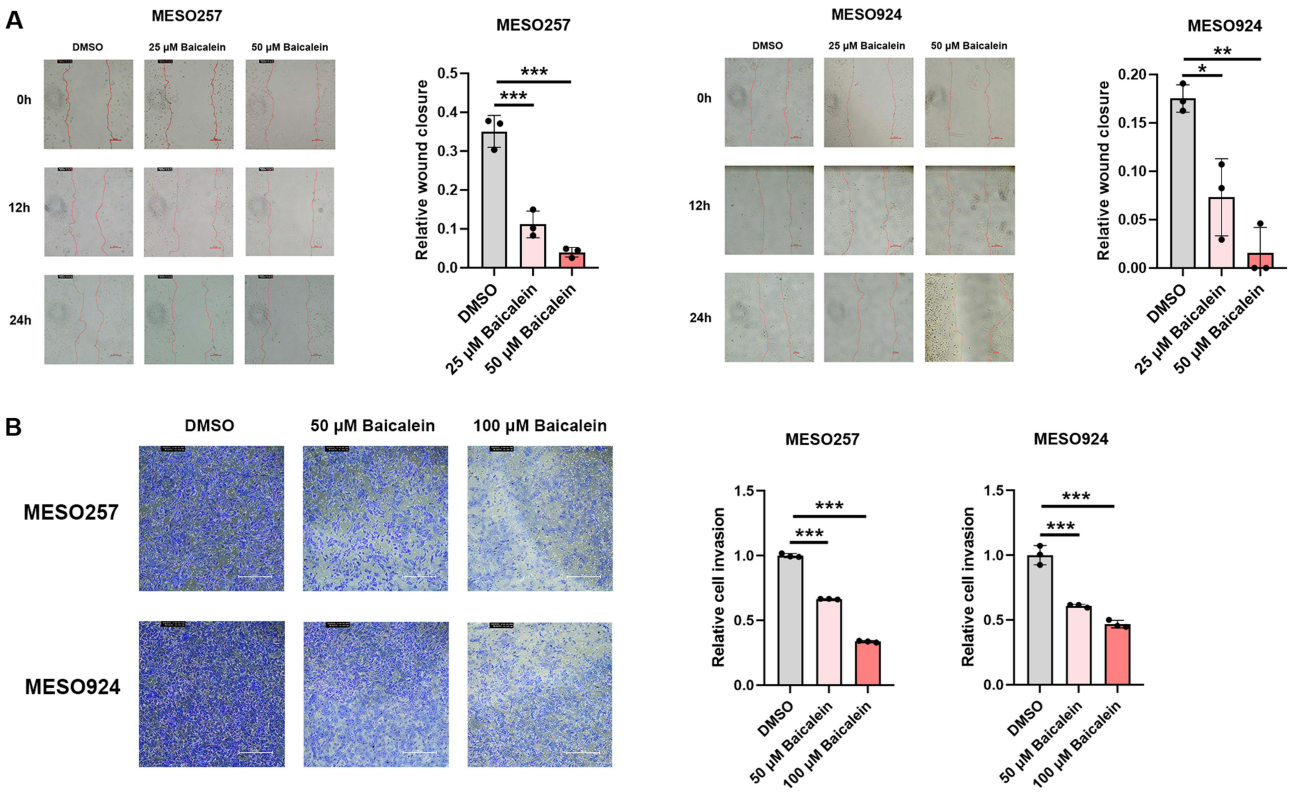

Figure 2 The regulatory role of baicalein on the migration and invasion of mesothelioma cells. (**A**) Baicalein inhibited migration of MESO257 and MESO924 after the treatment with baicalein for 12 h, as demonstrated by in vitro wound healing assays. The data were compared to the DMSO treatment and shown as mean (±SD; n = 3). Significant differences were defined as **P*< 0.05, ***P*< 0.01, ****P*< 0.001. (**B**) Baicalein inhibited invasion of MESO257 and MESO924 as assessed by matrigel invasion assays after the treatment with baicalein for 48 h. The data were normalized to the DMSO treatment and shown as mean (±SD; n = 3). Significant differences were defined as ****P*< 0.001.

and display coherent expression patterns.[22] To explore the signaling pathways involved in the antitumor activity of baicalein, we analyzed 50 hallmark gene sets. Our results revealed that 22 of these sets were enriched (Figure 3A). Notably, baicalein treatment activated the p53 signaling and apoptosis regulation pathways, while inhibiting pathways related to E2F targets, G2M checkpoint, mitotic spindle, angiogenesis, and epithelial-mesenchymal transition (Figure 3A). Next, we also conducted GSEA analyses to identify candidate transcription factors associated with the altered gene sets mediated by baicalein. The results indicated that FOXM1, a transcription factor known for its role in regulating the malignant phenotype of mesothelioma cells, was suppressed following baicalein treatment (Figure 3B).[23,24]

Additionally, we utilized the GPSA (genetic perturbation similarity analysis) database to identify potential causal perturbations from differentially expressed genes (DEGs) associated with baicalein treatment in mesothelioma cells.[25] The top 20 significantly enriched genes, such as YAP1, KIF20A, PPIG, RBM47, SREBF1, TCF3, BRG1, and FOXM1, were visually represented (Figure 3C). Importantly, we observed a strong correlation (Pearson correlation coefficient = 0.77) between baicalein and FOXM1 (Figure 3D). Together, the results from GPSA and transcription factor analyses suggest that FOXM1 may be a downstream target of baicalein in mesothelioma.

Given that p53 can negatively regulate FOXM1 expression, we hypothesize that the p53-FOXM1 signaling axis plays a crucial role in the antitumor efficacy of baicalein.[26,27] To investigate this further, we performed Western blotting assays to evaluate the expression of proteins related to the p53-FOXM1 pathway after treating mesothelioma cells (MESO257 and MESO924) with baicalein. The results showed that baicalein treatment increased p53 expression while decreasing FOXM1 and Cyclin B1 levels in a dose-dependent manner compared to the control group treated with DMSO (Figure 3E). These findings suggest that baicalein's effects on mesothelioma cell phenotype may be mediated through the p53-FOXM1 signaling axis.

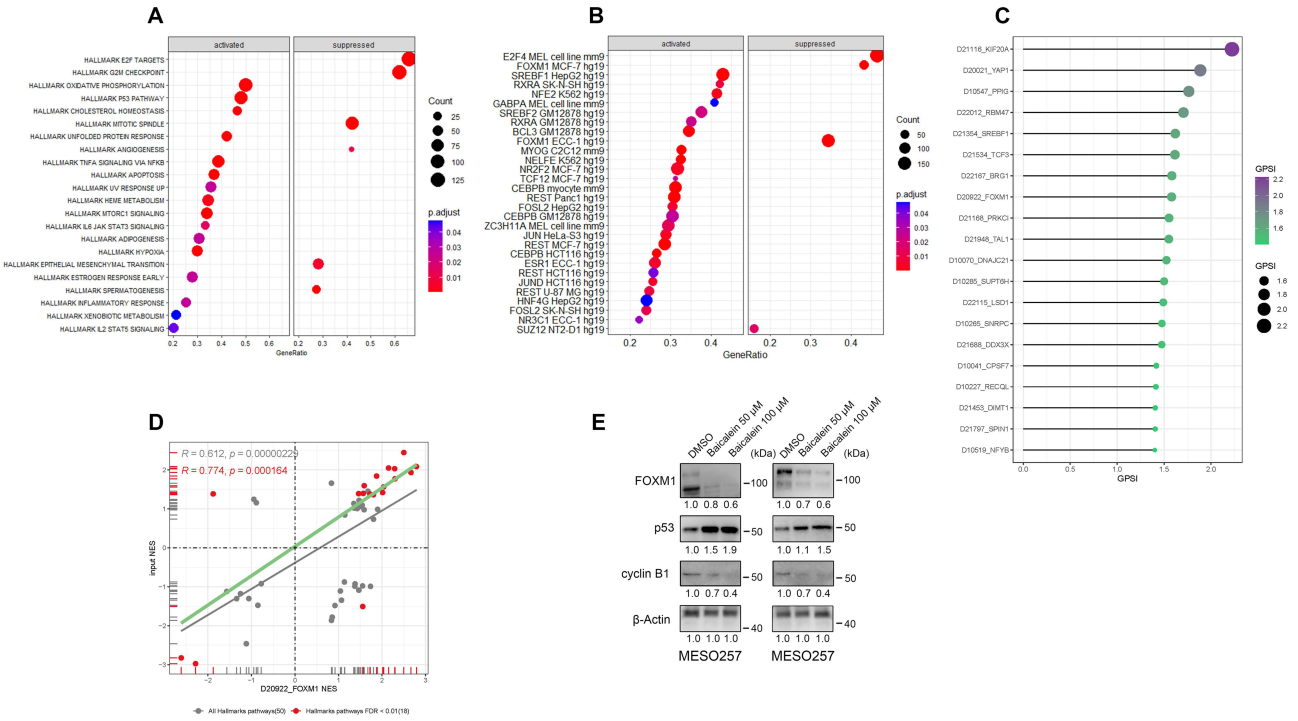

Figure 3 Effects of baicalein on the p53-FOXM1 signaling axis in mesothelioma cells. (**A**) The hallmarks gene sets enrichment analysis of baicalein treatment in mesothelioma cells. The size of the black circle represents the number of enriched genes, and the color of the circle represents the significance of gene enrichment. (**B**) The transcription factors enrichment analysis of baicalein. The size of the black circle represents the number of enriched genes, and the color of the circle represents the significance of gene enrichment. (**C**) The transcription factors that top20 enrichment leading edge genes related to baicalein based on the GPSAdb database. (**D**) Correlation coefficient between FOXM1 and baicalein based on the GPSAdb database. (**E**) Expression of p53, FOXM1, and cyclin B1 in MESO257 and MESO924 were assessed by immunoblotting after incubation with baicalein for 48 h. β-Actin staining is a loading control.

Baicalein Regulates the Proliferation, Apoptosis, Migration and Invasion of Mesothelioma Through FOXM1

To assess the role of the p53-FOXM1 axis in the tumor-suppressive effects mediated by baicalein, we conducted gain-of-function rescue experiments. Mesothelioma cells (MESO257 and MESO924) were transfected with FOXM1 overexpression plasmids, and the efficiency of overexpression was verified using RT-qPCR (Figure 4A). Treatment with baicalein significantly decreased cell viability in both cell lines compared to the control (Figure 4B). However, FOXM1 overexpression increased cell viability in MESO257 and MESO924 cells compared to controls (Figure 4B). Notably, FOXM1 overexpression also diminished the antiproliferative effects of baicalein in both cell lines (Figure 4B). We then performed caspase 3/7 activation assays to evaluate the impact of baicalein treatment and FOXM1 overexpression on cell apoptosis. The results showed that baicalein treatment significantly increased apoptosis compared to control cells (Figure 4C). Conversely, FOXM1 overexpression led to decreased apoptosis relative to the control (Figure 4C). Additionally, the increase in apoptosis induced by baicalein treatment was reduced in the presence of FOXM1 overexpression (Figure 4C). Next, assays of wound healing and matrigel invasion were performed to assess the impact of baicalein treatment and FOXM1 overexpression on cell migration and invasion respectively. Treatment with baicalein significantly decreased cell migration (Figure 4D) and invasion (Figure 4E) in both cell lines compared to the control. Meanwhile, FOXM1 overexpression increased cell migration (Figure 4D) and invasion (Figure 4E) in MESO257 and MESO924 cells compared to controls. However, the suppression in migration (Figure 4D) and invasion (Figure 4E) induced by baicalein treatment was attenuated in the presence of FOXM1 overexpression. These findings suggest that the reduced expression of FOXM1, at least in part, contributes to the effects of baicalein on the malignant phenotypic changes in mesothelioma cells. To provide an integrative overview of these findings, a schematic model was constructed to illustrate the proposed mechanism of baicalein in mesothelioma (Figure 5). As shown in the diagram, baicalein activates p53 signaling, which transcriptionally represses FOXM1, thereby promoting apoptosis and suppressing cell proliferation, migration,

https://doi.org/10.2147/CMAR.S551351

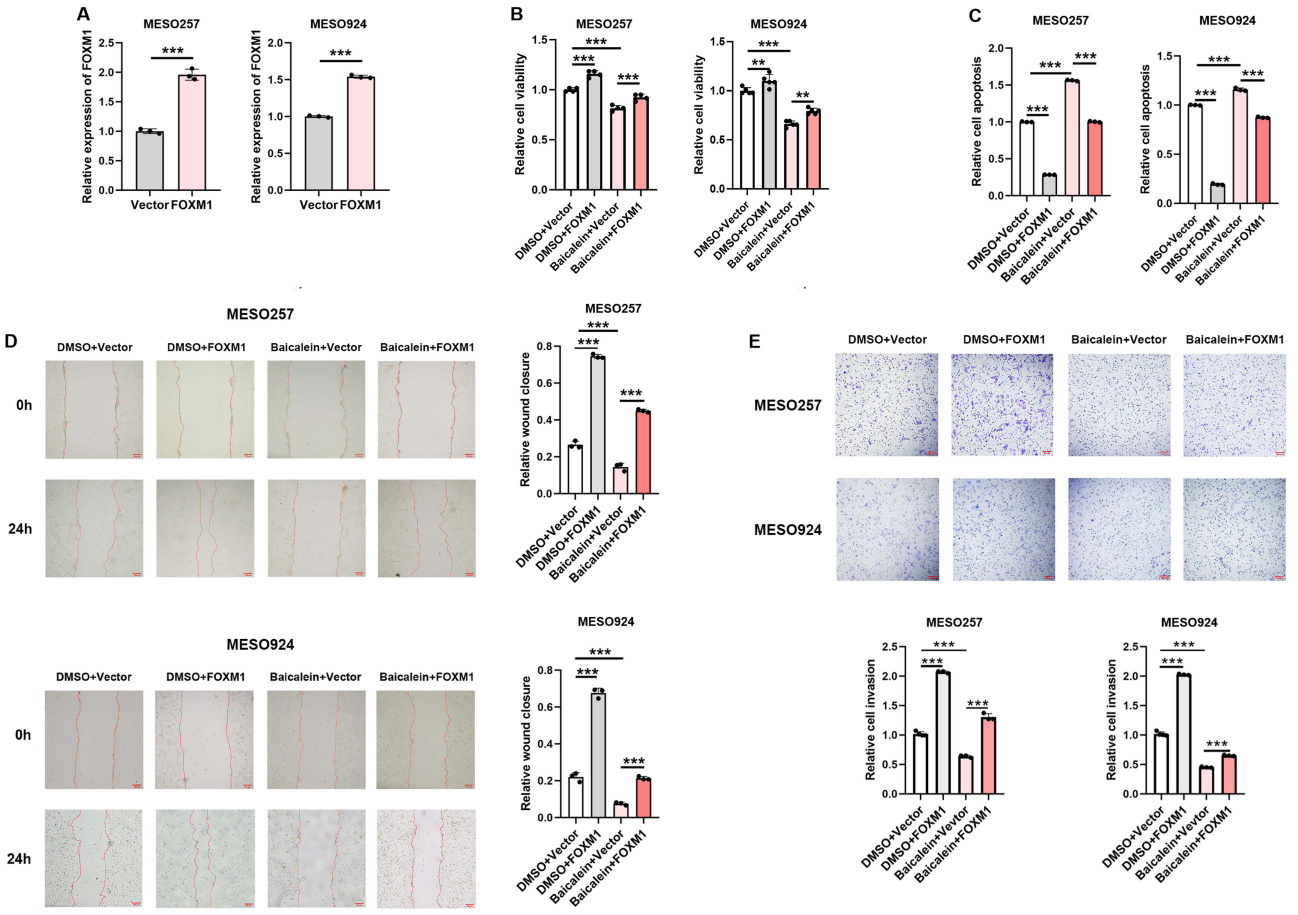

Figure 4 FOXM1 overexpression attenuated the anti-proliferation and pro-apoptosis of mesothelioma cells induced by baicalein. (**A**) The *FOXM1* transcript levels in MESO257 and MESO924 were determined by qRT-PCR after transfection with FOXM1-overexpressing plasmids for 24 h. The data were normalized to the vector treatment and shown as mean (±SD; n = 3). Significant differences were defined as ***P< 0.001. (**B**) Cell proliferation was assessed in MESO257 and MESO924 after transfection with FOXM1-overexpressing plasmids for 24 h and followed by baicalein treatment for 48 h. The data were normalized to the DMSO/vector treatment and shown as mean (±SD; n = 5). Significant differences were defined as **P< 0.01, ***P< 0.001. (**C**) Cell apoptosis was assessed in MESO257 and MESO924 after transfection with FOXM1-overexpressing plasmids for 24 h and followed by baicalein treatment for 48 h. The data were normalized to the DMSO/vector treatment and shown as mean (±SD; n = 3). Significant differences were defined as ***P< 0.001. (**D**) Cell migration was assessed in MESO257 and MESO924 after transfection with FOXM1-overexpressing plasmids for 24 h and followed by baicalein treatment for 12 h, as demonstrated by in vitro wound healing assays. The data were compared to the DMSO/vector treatment and shown as mean (±SD; n = 3). Significant differences were defined as ***P< 0.001. (**E**) Cell invasion was assessed in MESO257 and MESO924 after transfection with FOXM1-overexpressing plasmids for 24 h and followed by baicalein treatment for 48 h, as demonstrated by matrigel invasion assays. The data were compared to the DMSO/vector treatment and shown as mean (±SD; n = 3). Significant differences were defined as ***P< 0.001.

and invasion. Additionally, bioinformatic analyses suggested that oxidative phosphorylation-related and DNA damage-associated pathways may act upstream of p53 activation, providing a potential mechanistic link that warrants further investigation..

Discussion

Despite the development of various therapies, the mortality rate of mesothelioma remains alarmingly high. Current mainstream treatments often fail to achieve the desired effectiveness and can cause significant side effects. As a result, there is an urgent need for new drugs that do not exhibit obvious toxic side effects for mesothelioma patients. Traditional Chinese medicine has been widely recognized as an important complementary and alternative antitumor treatment in China, valued for its high efficacy, minimal toxicity, and affordability, and has played a vital role in cancer care for thousands of years.[28] Baicalein, a significant herbal medicine in traditional Chinese medicine, has been extensively used for its potential antitumor properties.[29] However, its effects on mesothelioma have not been previously reported. In this study, we demonstrate for the first time that baicalein reduces proliferation, migration, and invasion while promoting apoptosis and cell cycle arrest in mesothelioma cells (Figure 1–2). Furthermore, our findings suggest that the antitumor effects of baicalein might be regulated by the p53-FOXM1 signaling axis (Figure 3–4).

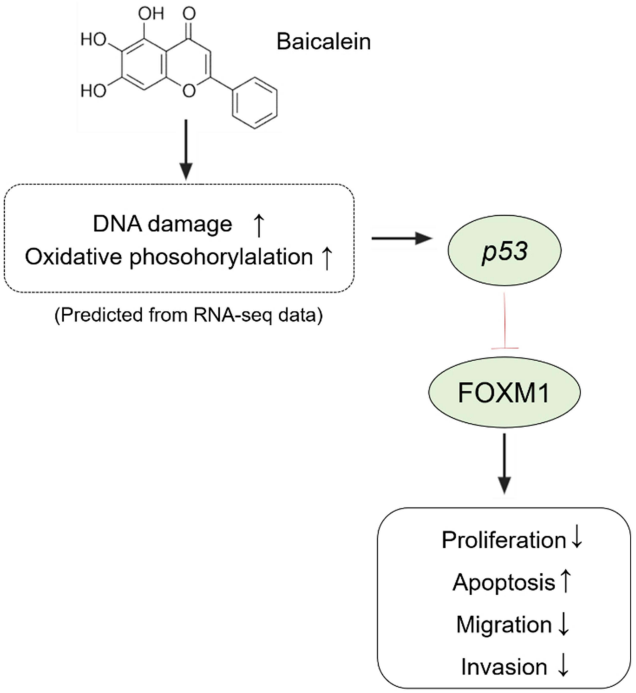

Figure 5 Schematic illustration of the proposed mechanism by which baicalein inhibits the progression of mesothelioma cells. Baicalein activates p53 signaling, leading to the repression of FOXM1. These molecular events collectively promote apoptosis and suppress mesothelioma cell proliferation, migration, and invasion. Black arrows denote activation, red blunt-ended lines denote inhibition, and dashed boxes represent bioinformatically predicted processes (oxidative phosphorylation and DNA damage).

To further clarify the rationale for cell line selection, MESO257 and MESO924 were chosen based on their well-characterized histological and molecular features. MESO257 exhibits an epithelioid phenotype, whereas MESO924 represents a biphasic subtype, together encompassing the most clinically relevant forms of malignant pleural mesothelioma.[14,15] Both cell lines have been extensively used in studies investigating receptor tyrosine kinase signaling and p53 reactivation, supporting their suitability for mechanistic analysis of the p53–FOXM1 axis targeted by baicalein. Notably, baicalein effectively suppressed proliferation and invasion and modulated the p53-FOXM1 pathway in both cell lines despite their distinct histological backgrounds, suggesting that its mechanism of action may be broadly applicable across mesothelioma subtypes.

We demonstrated that the p53-FOXM1 signaling axis is a crucial downstream target of baicalein (Figures 3–4). The protein p53 has garnered significant attention in oncology research due to its well-established role as a tumor suppressor in humans.[30] Dysregulation of p53, often through loss or mutation, increases the risk of cancer development. As a tumor suppressor, p53 primarily functions to inhibit the progression of cancer by interacting with various signaling pathways that are essential for key cellular processes, including cell division, maintenance of genomic stability, and apoptosis.[31] Redox reactions are vital for normal cellular function.[32] At the molecular level, oxygen metabolism underpins oxidative phosphorylation, which facilitates the production of reactive oxygen species (ROS).[33,34] These ROS play a role in pathogen killing by immune defenses mediated by innate immune cells.[35] However, excessive ROS can cause DNA damage, leading to the activation of the p53 pathway through the dissociation of MDM2-p53 complexes. This process allows p53 to enter the nucleus and enhance the transcription of downstream target genes involved in cell cycle arrest and apoptosis.[36] Previous studies have shown that p53 negatively regulates FOXM1 expression, and FOXM1 is involved in several cellular processes, including oxidative stress responses.[26,37,38] In our current study, KEGG analysis indicated that baicalein activates oxidative phosphorylation while inhibiting cell cycle progression (Table 1). Additionally, GSEA analysis based on 50 hallmark gene sets revealed that baicalein treatment suppressed the G2M checkpoint pathway while activating the apoptosis and p53 pathways in mesothelioma cells (Figure 3A). KEGG and GSEA analyses suggested enrichment of oxidative phosphorylation-related pathways and p53 activation after baicalein treatment. These transcriptomic signatures may be consistent with cellular stress responses, including potential ROS-associated DNA damage, which are known upstream regulators of p53 activation. However, these mechanisms were not directly examined in the

Table 1 Enriched Gene Sets of KEGG Analysis for Baicalein Treatment in Mesothelioma Cells by GSVA

ID	logFC	P.Value
RIBOSOME	1.04924547	2.18475E-09
AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM	0.79530319	7.8232E-07
NON_HOMOLOGOUS_END_JOINING	−0.72535424	5.97762E-06
DNA_REPLICATION	−0.65955228	2.64162E-05
SULFUR_METABOLISM	−0.6449481	4.92636E-05
SNARE_INTERACTIONS_IN_VESICULAR_TRANSPORT	0.60166028	8.74358E-05
BETA_ALANINE_METABOLISM	−0.61046686	8.97932E-05
RENIN_ANGIOTENSIN_SYSTEM	−0.63207109	9.22297E-05
OTHER_GLYCAN_DEGRADATION	0.61329917	0.000111398
CELL_CYCLE	−0.57092717	0.000167101
PRIMARY_BILE_ACID_BIOSYNTHESIS	−0.54494903	0.000407576
O_GLYCAN_BIOSYNTHESIS	−0.51115408	0.00067081
THYROID_CANCER	0.52279666	0.000727234
BUTANOATE_METABOLISM	−0.51484795	0.001009147
PROTEIN_EXPORT	0.49143167	0.001828909
LYSOSOME	0.46483499	0.002034627
TRYPTOPHAN_METABOLISM	−0.45766774	0.002725065
MISMATCH_REPAIR	−0.44207261	0.0029404
ECM_RECEPTOR_INTERACTION	−0.44348778	0.003546392
LYSINE_DEGRADATION	−0.4262905	0.004238994
PARKINSONS_DISEASE	0.47746334	0.004276764
OXIDATIVE_PHOSPHORYLATION	0.47941157	0.004350078
VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	−0.40990338	0.00580751
PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	−0.41960947	0.005869353
FATTY_ACID_METABOLISM	−0.42731267	0.006040271
VIBRIO_CHOLERAE_INFECTION	0.40978595	0.006416176
REGULATION_OF_AUTOPHAGY	0.40374152	0.00651575
STEROID_BIOSYNTHESIS	0.40306967	0.007765028
GALACTOSE_METABOLISM	0.39752533	0.00898911
HOMOLOGOUS_RECOMBINATION	−0.3965101	0.010932381
RETINOL_METABOLISM	−0.3567965	0.016240433
N_GLYCAN_BIOSYNTHESIS	0.35002851	0.016981188
ASCORBATE_AND_ALDARATE_METABOLISM	−0.36660721	0.017703731
ALZHEIMERS_DISEASE	0.36378211	0.019180311
PENTOSE_PHOSPHATE_PATHWAY	0.33564993	0.021496495
CARDIAC_MUSCLE_CONTRACTION	0.33049264	0.024732907
SMALL_CELL_LUNG_CANCER	−0.33282182	0.025223971
GLIOMA	−0.33182303	0.025910773
OLFACTORY_TRANSDUCTION	−0.31868817	0.028532903
HUNTINGTONS_DISEASE	0.33339921	0.029570615
TERPENOID_BACKBONE_BIOSYNTHESIS	0.33491768	0.032072215
NICOTINATE_AND_NICOTINAMIDE_METABOLISM	0.32286092	0.032280482
GLYCINE_SERINE_AND_THREONINE_METABOLISM	0.31852241	0.032585255
GLYCOSAMINOGLYCAN_DEGRADATION	0.35712007	0.033171977
SPLICEOSOME	−0.32486794	0.034495314
PROPANOATE_METABOLISM	−0.3203531	0.034667688
GLYCOSPHINGOLIPID_BIOSYNTHESIS_LACTO_AND_NEOLACTO_SERIES	0.29891608	0.040175168
PATHOGENIC_ESCHERICHIA_COLI_INFECTION	−0.30421625	0.041872345

(*Continued*)

Table 1 (Continued).

ID	logFC	P.Value
GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.31362707	0.043508497
BASAL_CELL_CARCINOMA	−0.29562171	0.043896551

Notes: Table 1 displays significantly enriched KEGG pathways in mesothelioma cells following baicalein treatment, identified by Gene Set Variation Analysis (GSVA). Pathways were ranked by nominal P value. logFC represents the log2-fold change in pathway activity, where positive values indicate upregulation and negative values indicate downregulation by baicalein. A selection of top significantly altered pathways ($P < 0.05$) is shown.

present study and therefore remain speculative. Future studies incorporating ROS measurement, γH2AX detection, and antioxidant rescue will be required to determine whether oxidative stress contributes to baicalein-mediated p53-FOXM1 modulation. Thus, our results suggest that DNA damage induced by oxidative phosphorylation after baicalein treatment, leading to the activation of the p53-FOXM1 signaling axis, may be one of the mechanisms through which baicalein promotes apoptosis and suppresses cell division, particularly in the G2/M phase.

Epithelial-mesenchymal transition (EMT) is a critical physiological process characterized by the loss of epithelial traits and the acquisition of mesenchymal features in cells. Previous studies have shown that EMT plays vital roles in various tumor functions, including cancer progression and metastasis.[39] In our study, we found that baicalein treatment reduced the migration and invasion of mesothelioma cells (Figure 2). Notably, baicalein treatment also inhibited the EMT pathway (Figure 3A), aligning with previous findings that highlight the importance of EMT signaling in the development and metastasis of malignant pleural mesothelioma.[34] These results suggest that baicalein may exert an anti-metastatic effect by suppressing the EMT signaling pathway. While direct experimental evidence for baicalein's inhibition of the EMT pathway was not established in this work, our findings indicate that baicalein could be a promising therapeutic option for patients with metastatic mesothelioma.

The IL-6/JAK/STAT3 pathway, STAT5 pathway, and TNF-α signaling via the NF-κB pathway are abnormally activated in several cancers, promoting proliferation, invasion, and metastasis while inducing apoptosis in cancer cells.[40–42] In our study, we found that baicalein treatment activated the IL-6/JAK/STAT3 signaling, STAT5 signaling, and TNF-α signaling via the NF-κB pathway (Figure 3A). This finding contrasts with previous research indicating that baicalein functions as an anti-tumor agent by inhibiting TNF-α-induced NF-κB activation,[38] IL-6/STAT3 signaling, and JAK2/STAT5 signaling in cervical cancer, breast cancer, and chronic myeloid leukemia, respectively.[12,43] A possible explanation for this might be that mesothelioma cells activated these carcinogenic signaling pathways to cope with the challenges of survival stress induced by baicalein, and eventually achieved victory by developing the resistance to baicalein. These interesting findings revealed the "multi-face" roles of baicalein in the regulation of cancer-related molecular mechanisms in a cancer-type-dependent manner. Notably, our results showed that baicalein treatment led to the suppression of the spliceosome pathway induced by the DNA replication stress (Table 1), and then triggered an antiviral (viral mimicry) immune response, which might through the activation of an important immune-related pathway termed tumor necrosis factor-α signaling via NF-κB pathways.[44,45]

The present study yielded several important findings; however, there are notable limitations that should be acknowledged. Firstly, while our results demonstrated that multiple well-known signaling pathways related to mesothelioma progression were modulated by baicalein, we focused primarily on the p53-FOXM1 signaling axis. Other pathways and target genes may also play significant roles in the anti-tumor effects of baicalein. Therefore, further research is needed to confirm the regulatory effects of baicalein on these identified cancer-related pathways. Secondly, as in vitro experiments often do not accurately reflect in vivo conditions, it is crucial to investigate the roles and mechanisms of baicalein in mesothelioma cells using in vivo models in future studies.

Conclusion

Baicalein inhibited proliferation, migration, and invasion while promoting apoptosis and cell-cycle arrest in human mesothelioma cells in vitro. Mechanistically, baicalein activated p53 and downregulated FOXM1 within the p53-FOXM1 signaling axis. Overexpression of FOXM1 partially reversed the antiproliferative and proapoptotic effects of baicalein, indicating that this pathway plays a pivotal role in mediating its antitumor activity. Collectively, these findings suggest

that baicalein represents a promising lead compound for the development of novel therapeutic strategies against mesothelioma, warranting further validation in preclinical and in vivo models.

Acknowledgments

We thank all the staff who participated in this study, especially the MSigDB database for kindly providing valuable data resources (https://www.gsea-msigdb.org/gsea/index.jsp).

Author Contributions

Wen-Fei Xu and Xu-Hu Li are co-corresponding authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Zhejiang Provincial Natural Science Foundation of China (LQ23H160002), the Shihezi City Scientific and Technological Development Program (2024SF08), the Collaborative Project with China Resources Research Institute of Science and Technology (ILH24001), Innovation Guidance Special Program for New-type Research and Development Institutions in Jiaxing (NO. 2025YDZX028), and the Yangtze Delta Region Institute of Tsinghua University, Zhejiang (LZZLX23C002).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Craighead JE, Mossman BT. The pathogenesis of asbestos-associated diseases. *New Engl J Med*. 1982;306(24):1446–1455. doi:10.1056/NEJM198206173062403
2. Carbone M, Pass HI, Rizzo P, et al. Simian virus 40-like DNA sequences in human pleural mesothelioma. *Oncogene*. 1994;9(6):1781–1790.
3. Müller-Hermelink HK, Engel P, Kuo T, et al. Pathology & genetics, tumours of the lung, pleura, thymus and heart. *WHO Blue Books*. 2004;146–147.
4. Yao C, Zhang J, Li J, et al. Traditional Chinese medicine (TCM) as a source of new anticancer drugs. *Nat Prod Rep*. 2021;38(9):1618–1633. doi:10.1039/D0NP00057D
5. Li-Weber M. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. *Cancer Treat Rev*. 2009;35(1):57–68. doi:10.1016/j.ctrv.2008.09.005
6. Rahmani AH, Almatroudi A, Khan AA, et al. The multifaceted role of baicalein in cancer management through modulation of cell signalling pathways. *Molecules*. 2022;27(22):8023. doi:10.3390/molecules27228023
7. Ma GZ, Liu CH, Wei B, et al. Baicalein inhibits DMBA/TPA-induced skin tumorigenesis in mice by modulating proliferation, apoptosis, and inflammation. *Inflammation*. 2013;36(2):457–467. doi:10.1007/s10753-012-9566-y
8. Kim DH, Hossain MA, Kang YJ, et al. Baicalein, an active component of *Scutellaria baicalensis* Georgi, induces apoptosis in human colon cancer cells and prevents AOM/DSS-induced colon cancer in mice. *Int J Oncol*. 2013;43(5):1652–1658. doi:10.3892/ijo.2013.2086
9. Phan T, Nguyen VH, Salazar MA, et al. Inhibition of autophagy amplifies baicalein-induced apoptosis in human colorectal cancer. *Mol Ther Oncolytics*. 2020;19:1–7. doi:10.1016/j.omto.2020.08.016
10. Lee HZ, Leung HWC, Lai MY, et al. Baicalein induced cell cycle arrest and apoptosis in human lung squamous carcinoma CH27 cells. *Anticancer Res*. 2005;25(2A):959–964.
11. Park YG, Choi J, Jung HK, et al. Baicalein inhibits tumor progression by inhibiting tumor cell growth and tumor angiogenesis. *Oncol Rep*. 2017;38(5):3011–3018. doi:10.3892/or.2017.6007
12. Susmitha GD, Miyazato K, Ogura K, et al. Anti-metastatic effects of baicalein by targeting STAT3 activity in breast cancer cells. *Biol Pharm Bull*. 2020;43(12):1899–1905. doi:10.1248/bpb.b20-00571
13. Yan W, Ma X, Zhao X, Zhang S. Baicalein induces apoptosis and autophagy of breast cancer cells via inhibiting PI3K/AKT pathway in vivo and vitro. *Drug Des Dev Ther*. 2018;12:3961–3972. doi:10.2147/DDDT.S181939
14. Mizuno T, Murakami H, Fujii M, et al. YAP induces malignant mesothelioma cell proliferation by upregulating transcription of cell cycle-promoting genes. *Oncogene*. 2012;31(49):5117–5122. doi:10.1038/onc.2012.5
15. Endo I, Amatya VJ, Kushitani K, et al. FOXM1 promotes mesothelioma cell migration and invasion via activation of SMAD signaling. *Anticancer Res*. 2023;43(9):3961–3968. doi:10.21873/anticanres.16583
16. Pandit B, Halasi M, Gartel AL. p53 negatively regulates expression of FoxM1. *Cell Cycle*. 2009;8(20):3425–3427. doi:10.4161/cc.8.20.9628
17. Ou WB, Hubert C, Fletcher JA, et al. Targeted inhibition of multiple receptor tyrosine kinases in mesothelioma. *Neoplasia*. 2011;13(1):12–IN2. doi:10.1593/neo.101156

18. Ou WB, Lu M, Eilers G, et al. Co-targeting of FAK and MDM2 triggers additive anti-proliferative effects in mesothelioma via a coordinated reactivation of p53. *Br J Cancer*. 2016;115(10):1253–1263. doi:10.1038/bjc.2016.331
19. Shaw RJ, Paez JG, Curto M, et al. The Nf2 tumor suppressor, merlin, functions in Rac-dependent signaling. *Dev Cell*. 2001;1(1):63–72. doi:10.1016/S1534-5807(01)00009-0
20. Yang MH, Chang SY, Chiou SH, et al. Overexpression of NBS1 induces epithelial–mesenchymal transition and co-expression of NBS1 and Snail predicts metastasis of head and neck cancer. *Oncogene*. 2007;26(10):1459–1467. doi:10.1038/sj.onc.1209929
21. Yu G, Wang LG, Han Y, et al. clusterProfiler: an R package for comparing biological themes among gene clusters. *Omics*. 2012;16(5):284–287. doi:10.1089/omi.2011.0118
22. Payne RW. Wiley interdisciplinary reviews: computational statistics. *Genstat*. 2009;1:255–1258.
23. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res*. 2001;61(22):8118–8121.
24. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *P Natl a Sci*. 2005;102(43):15545–15550. doi:10.1073/pnas.0506580102
25. Liberzon A, Birger C, Thorvaldsdóttir H, et al. The molecular signatures database hallmark gene set collection. *Cell Syst*. 2015;1(6):417–425. doi:10.1016/j.cels.2015.12.004
26. Guo S, Xu Z, Dong X, et al. GPSAdb: a comprehensive web resource for interactive exploration of genetic perturbation RNA-seq datasets. *Nucleic Acids Res*. 2023;51(D1):D964–D968. doi:10.1093/nar/gkac1066
27. Barsotti AM, Prives C. Pro-proliferative FoxM1 is a target of p53-mediated repression. *Oncogene*. 2009;28(48):4295–4305. doi:10.1038/onc.2009.282
28. Efferth T, Li PC, Konkimalla VSB, Kaina BJ. From traditional Chinese medicine to rational cancer therapy. *Trends Mol Med*. 2007;13(8):353–361. doi:10.1016/j.molmed.2007.07.001
29. Verma E, Kumar A, Daimary UD, et al. Potential of baicalein in the prevention and treatment of cancer: a scientometric analyses based review. *J Funct Foods*. 2021;86:104660.
30. Carson DA, Lois A. Cancer progression and p53. *Lancet*. 1995;346(8981):1009–1011. doi:10.1016/S0140-6736(95)91693-8
31. Hafner A, Bulyk ML, Jambhekar A, et al. The multiple mechanisms that regulate p53 activity and cell fate. *Nat Rev Mol Cell Bio*. 2019;20(4):199–210. doi:10.1038/s41580-019-0110-x
32. McCord JM. The evolution of free radicals and oxidative stress. *Am J Med*. 2000;108(8):652–659. doi:10.1016/S0002-9343(00)00412-5
33. Sabharwal SS, Schumacker PT. Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? *Nat Rev Cancer*. 2014;14(11):709–721. doi:10.1038/nrc3803
34. Shadel GS, Horvath TL. Mitochondrial ROS signaling in organismal homeostasis. *Cell*. 2015;163(3):560–569. doi:10.1016/j.cell.2015.10.001
35. Khan AA, Alsahli MA, Rahmani AH. Myeloperoxidase as an active disease biomarker: recent biochemical and pathological perspectives. *Med Sci*. 2018;6(2):33.
36. Meek DW. Tumour suppression by p53: a role for the DNA damage response? *Nat Rev Cancer*. 2009;9(10):714–723. doi:10.1038/nrc2716
37. Raychaudhuri P, Park HJ. FoxM1: a master regulator of tumor metastasis. *Cancer Res*. 2011;71(13):4329. doi:10.1158/0008-5472.CAN-11-0640
38. Park HJ, Carr JR, Wang Z, et al. FoxM1, a critical regulator of oxidative stress during oncogenesis. *EMBO J*. 2009;28(19):2908–2918. doi:10.1038/emboj.2009.239
39. Pastushenko I, Blanpain C. EMT transition states during tumor progression and metastasis. *Trends Cell Biol*. 2019;29(3):212–226. doi:10.1016/j.tcb.2018.12.001
40. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol*. 2018;15(4):234–248. doi:10.1038/nrclinonc.2018.8
41. Halim CE, Deng S, Ong MS, et al. Involvement of STAT5 in oncogenesis. *Biomedicines*. 2020;8(9):316. doi:10.3390/biomedicines8090316
42. Lin Y, Bai L, Chen W, Xu S. The NF-κB activation pathways, emerging molecular targets for cancer prevention and therapy. *Expert Opin Ther Tar*. 2010;14(1):45–55. doi:10.1517/14728220903431069
43. Xu X, Ji S, Chen Y, et al. Induction of DNMT1-dependent demethylation of SHP-1 by the natural flavonoid compound Baicalein overcame Imatinib-resistance in CML CD34+ cells. *Cell Commun Signal*. 2023;21(1):47. doi:10.1186/s12964-023-01049-9
44. Bowling EA, Wang JH, Gong F, et al. Spliceosome-targeted therapies trigger an antiviral immune response in triple-negative breast cancer. *Cell*. 2021;184(2):384–403.e21. doi:10.1016/j.cell.2020.12.031
45. Shen JZ, Qiu Z, Wu Q, et al. FBXO44 promotes DNA replication-coupled repetitive element silencing in cancer cells. *Cell*. 2021;184(2):352–369.e23. doi:10.1016/j.cell.2020.11.042

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