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Original Article

Corylin attenuates oral squamous cell carcinoma progression through c-Myc inhibition

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KEYWORDS
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Epithelial–mesenchymal transition (EMT);
Combination therapy

Abstract *Background: /purpose*: Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy of the head and neck, with current treatment options often limited by low efficacy and drug resistance. In this study, we investigated the anticancer activity and underlying mechanisms of corylin, a flavonoid extracted from Psoralea corylifolia, in OSCC.
Materials and methods: OSCC cell lines (SAS and OECM1) were treated with corylin, and its effects on cell proliferation, migration, and invasion were assessed using cell function assays. Flow cytometry and DiOC6/PI staining were performed to analyze cell cycle progression and apoptosis, while Western blotting was used to elucidate the molecular mechanisms of corylin's action.
Results: Corylin selectively inhibited OSCC cell growth, migration, and invasion while exhibiting minimal toxicity toward normal human cells. Mechanistic investigations revealed that corylin downregulated c-Myc expression, which subsequently modulated the expression of cell

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cycle checkpoint regulators, apoptosis-related proteins, and epithelial–mesenchymal transition (EMT)-associated markers. This led to G1 phase cell cycle arrest and enhanced apoptosis induction. Additionally, corylin significantly enhanced the anticancer efficacy of cisplatin and 5-FU in OSCC cells.

Conclusion: Corylin exhibits potent anticancer activity against OSCC by targeting c-Myc-mediated oncogenic pathways and may serve as a promising therapeutic candidate. Furthermore, its ability to synergize with cisplatin and 5-FU suggests its potential role in combination therapy to improve treatment efficacy.

Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy of the head and neck, accounting for over 90 % of all oral cancer cases.[1,2] With an estimated 370,000 new cases and 170,000 deaths reported annually worldwide, OSCC remains a significant global health challenge.[3] The incidence of OSCC is particularly high in Southeast Asia, South Asia, and South America, largely attributed to well-established risk factors such as betel nut chewing, tobacco smoking, excessive alcohol consumption, and persistent infection with human papillomavirus (HPV).[4–6] Despite advances in multimodal treatment approaches, including surgical resection, radiotherapy, and chemotherapy, the prognosis of OSCC patients remains unsatisfactory due to its high recurrence rate, aggressive invasion, and intrinsic drug resistance. Notably, approximately 40 % of patients experience tumor recurrence within three years following surgical intervention, underscoring the urgent need for novel therapeutic strategies with improved efficacy and reduced toxicity.[7,8]

One of the critical oncogenes implicated in OSCC pathogenesis is c-Myc, a transcription factor that governs multiple hallmarks of cancer, including uncontrolled proliferation, metabolic reprogramming, evasion of apoptosis, genomic instability, and immune evasion.[9,10] c-Myc belongs to the basic-helix-loop-helix-leucine zipper (bHLHZip) transcription factor family and exerts its oncogenic effects by regulating a vast array of target genes involved in cell cycle progression, DNA repair, angiogenesis, protein synthesis, and stem cell maintenance.[11–14] Aberrant overexpression of c-Myc is observed in approximately 70 % of human cancers, including OSCC, and is strongly correlated with poor prognosis, increased metastatic potential, and resistance to chemotherapy and radiotherapy.[9,15,16] Given its central role in tumorigenesis and therapy resistance, c-Myc has emerged as an attractive target for cancer treatment.[14] However, direct pharmacological inhibition of c-Myc has proven challenging due to its intrinsically disordered protein structure and widespread involvement in essential cellular processes.[17] Therefore, alternative strategies aimed at suppressing c-Myc activity, such as targeting its upstream regulators or downstream effectors, are currently being explored as potential therapeutic approaches.

Psoralea corylifolia, a traditional medicinal herb widely utilized in Southeast Asia, has been reported to exhibit anti-inflammatory, antioxidant, and anticancer properties.[18] Among its bioactive constituents, the flavonoid corylin has garnered significant attention for its potent anticancer potential through the modulation of critical cellular signaling pathways. Studies have demonstrated that corylin can suppress the progression of non-small cell lung cancer by targeting p65 and modulating the NF-κB signaling pathway.[19] Additionally, corylin inhibits the proliferation and metastasis of breast cancer and hepatocellular carcinoma cells through the regulation of non-coding RNAs such as miR-34c, LINC00963, and lncRNA-GAS5.[20,21] Recent findings also indicate that corylin can impede the development of osteosarcoma by suppressing the HMGB1/p38 MAPK signaling pathway.[22] However, its potential therapeutic efficacy and underlying mechanisms in oral squamous cell carcinoma (OSCC) remain largely unexplored. Given the urgent need for effective therapeutic strategies for OSCC, this study investigates the anticancer effects of corylin and its underlying mechanisms, with a focus on c-Myc inhibition. We also evaluate its potential to enhance the efficacy of conventional chemotherapeutics, aiming to support the development of corylin as a novel therapeutic or adjuvant agent for OSCC.

Materials and methods

Cell lines and culture conditions

Human oral squamous cell carcinoma (OSCC) cell lines OECM1 and SAS were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA), while normal human fibroblasts (HFF3) were generously provided by Professor Tzu-Chien V. Wang (Chang Gung University, Taiwan). All cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % fetal bovine serum (FBS) and maintained at 37 °C in a humidified incubator with 5 % CO_2.

Reagents and antibodies

Corylin (≥98 % purity, verified by HPLC) was purchased from Shanghai BS Bio-Tech Co., Ltd. (Shanghai, China). Primary antibodies against c-Myc (#5605), p21 (#2947), CDC25A (#3652), cyclin D1 (#2978), CDK4 (#12790), and Bcl-2 (#2876) were purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA). Additional primary antibodies against N-cadherin (#127345), E-cadherin (#100443), vimentin (#100619), snail (#100754), and β-actin (#109639)

were obtained from GeneTex, Inc. (Irvine, CA, USA). Secondary antibodies were acquired from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA).

Western blot analysis

Cells were treated with varying concentrations of corylin for 24 or 48 h, then harvested, washed twice with phosphate-buffered saline (PBS), and lysed in 150 μL of radioimmunoprecipitation assay (RIPA) buffer containing protease inhibitors. Protein extracts (30 μg per sample) were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes. Immunoblotting was performed using the specified primary and secondary antibodies. Protein bands were visualized using an enhanced chemiluminescence (ECL) detection system (Thermo Fisher Scientific, Waltham, MA, USA) and captured with UVP ChemStudio Imaging Systems (Analytik Jena, Thuringia, Germany). Band intensities were quantified using ImageQuant 5.2 software (GE Healthcare, Waukesha, WI, USA).

Cell proliferation assay

Cell proliferation was monitored using the xCELLigence Real-Time Cell Analyzer (Roche Life Science, Indianapolis, IN, USA) following the manufacturer's instructions. In brief, 1.2×10^4 SAS or OECM1 cells were seeded into 8-well E-plates and cultured in DMEM containing various concentrations of corylin or vehicle control. Real-time cell impedance measurements were recorded over a 72-h period, and the results were expressed as the cell index (CI).

Cell migration assay

Cell migration capacity was assessed using wound-healing and Transwell migration assays, performed as previously described.[23] Briefly, the wound healing assay was performed using culture inserts to generate a uniform cell-free gap. SAS and OECM1 cells were seeded into culture inserts (Ibidi, Martinsried, Germany) placed in 6-well plates at a density ensuring confluency. After overnight incubation, the inserts were gently removed to create a standardized 500-μm-wide cell-free gap. Detached cells were washed away with PBS, and the remaining adherent cells were cultured in serum-free DMEM containing varying concentrations of corylin or vehicle control. Phase-contrast images of the wound area were captured at 0, 4, 8, and 24 h using an inverted microscope (Olympus, Tokyo, Japan). For the Transwell migration assay, cells were seeded in serum-free medium in the upper chamber of Transwell inserts, while complete medium containing 10 % FBS was added to the lower chamber. After incubation, non-migrated cells were removed, and migrated cells were fixed, stained, and quantified.

Cell invasion assay

Cell invasion ability was evaluated using a Matrigel-coated Transwell invasion assay, conducted as previously reported.[23] In brief, cells were seeded into the upper chamber of Transwell inserts pre-coated with Matrigel, while the lower chamber contained DMEM supplemented with 10 % FBS. After incubation, invasive cells were fixed, stained, and counted under a microscope.

Cell apoptosis assay and flow cytometry

To assess apoptosis, cells were treated with different concentrations of corylin for 24 h, harvested, and fixed in 100 % ethanol for 10 min. Apoptotic cells were detected using the Alexa Fluor® 488 Annexin V/Dead Cell Apoptosis Kit (Thermo Fisher Scientific) and $DiOC_6$/PI double staining, following the manufacturer's protocol. Flow cytometric analysis was performed using a BD FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

Cell cycle analysis

For cell cycle analysis, treated cells were harvested via trypsinization, washed with PBS, and fixed in 70 % ethanol on ice for 1 h. The fixed cells were then stained with a solution containing 50 μg/mL propidium iodide (PI) and 100 μg/mL RNase A. DNA content was analyzed using a FACSCalibur flow cytometer (BD Biosciences), and data were processed with CellQuest Pro software (BD Biosciences).

Data analysis

All experiments were independently performed in triplicate. Data are presented as mean ± standard deviation (SD). Statistical comparisons were conducted using SPSS v16.0 or Microsoft Excel 2007, with significance defined as $P < 0.05$ (*), $P < 0.01$ (**), and $P < 0.001$ (***).

Results

Corylin inhibits OSCC cell proliferation, migration, and invasion

To assess the inhibitory effects of corylin on OSCC cells and determine its effective dosage, SAS and OECM1 cells were treated with increasing concentrations of corylin. Cell viability assays revealed that corylin significantly suppressed OSCC cell proliferation in a dose-dependent manner, with half-maximal inhibitory concentration (IC_{50}) values of 36.22 μM and 37.09 μM in OECM1 and SAS cells, respectively (Fig. 1A and B).

Since the highly invasive nature of OSCC is a major factor contributing to poor prognosis, we further investigated the effects of corylin on cell migration and invasion using wound healing, Transwell migration and invasion assays. The results demonstrated that corylin markedly inhibited OSCC cell motility and invasiveness, with stronger suppression observed at higher concentrations (Fig. 1D–J). To determine the selectivity of corylin's anticancer effects, we examined its cytotoxicity in human fibroblast (HFF) cells. Notably, corylin exhibited minimal toxicity toward normal fibroblasts at lower concentrations, with significant

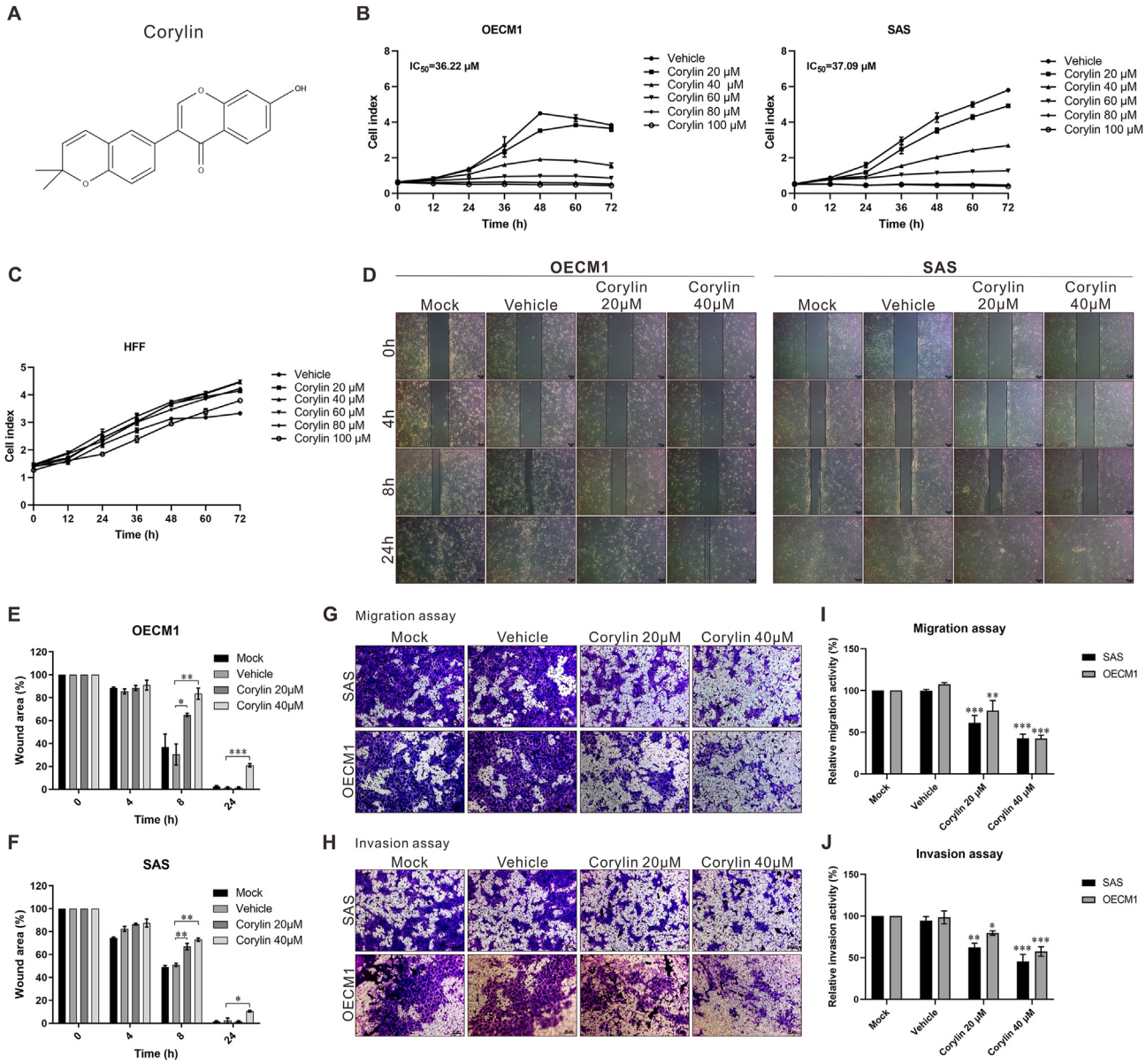

Figure 1 Corylin attenuates proliferation, migration, and invasion of OSCC cells. (A) Chemical structure of corylin. (B, C) Real-time analysis of OECM1, SAS, and HFF cell proliferation following treatment with increasing concentrations of corylin, assessed using the xCELLigence RTCA system. (D) Representative images of wound healing assays evaluating the impact of corylin on OSCC cell motility. (E, F) Quantitative analysis of wound closure rates. (G, H) Transwell migration and invasion assays demonstrating the inhibitory effects of corylin on OSCC cell motility. (I, J) Quantification of migrated and invaded cells. All experiments were performed in three independent biological replicates. Results are presented as mean ± SD, with statistical significance determined by Student's t-test. Statistical significance compared to vehicle (DMSO) control: $P < 0.01$ (**), $P < 0.001$ (***).

growth inhibition only at high doses, indicating that corylin selectively targets OSCC cells (Fig. 1C).

Corylin suppresses c-Myc expression in OSCC cells

c-Myc is frequently overexpressed in oral squamous cell carcinoma (OSCC) and various other malignancies, where it plays a pivotal role in driving tumor progression, metastasis, resistance to apoptosis, and therapeutic resistance.[10] To further elucidate the clinical relevance of c-Myc in OSCC, we performed a comprehensive analysis utilizing data from The Cancer Genome Atlas (TCGA). Our findings revealed that c-Myc is significantly overexpressed in the majority of head and neck squamous cell carcinoma (HNSCC) specimens and is strongly associated with disease onset and patient prognosis (Fig. 2A and B). Notably, elevated c-Myc expression was correlated with a significantly reduced overall survival rate, highlighting its potential as a prognostic biomarker and a key contributor to HNSCC progression.

To investigate whether corylin modulates c-Myc expression, we treated OSCC cells with different concentrations of

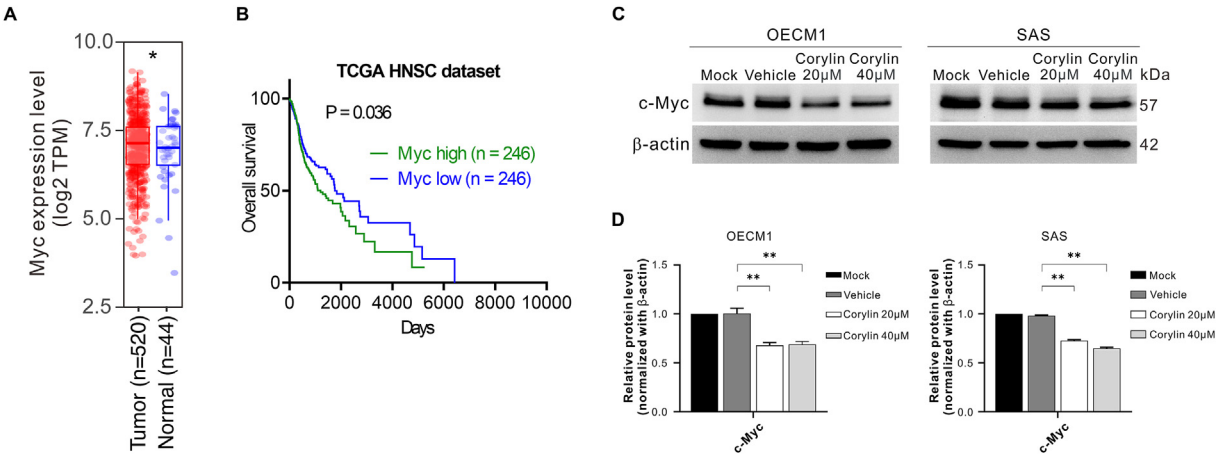

Figure 2 Corylin inhibits c-Myc expression in OSCC cells. (A) Differential expression of MYC in head and neck squamous cell carcinoma (HNSCC) versus normal tissues, analyzed from TCGA dataset. TPM: transcripts per million. (B) Kaplan—Meier survival analysis of HNSCC patients stratified by MYC expression (TCGA). (C) Western blot analysis showing reduced c-Myc protein levels in OSCC cells after corylin treatment. (D) Quantification of Western blot results from three independent experiments. Results are presented as mean ± SD, with statistical significance determined by Student's t-test. Statistical significance versus vehicle control: $P < 0.01$ (**).

corylin and performed Western blot analysis. The results showed that c-Myc protein levels were significantly reduced in both OECM1 and SAS cells following corylin treatment compared to the vehicle control (Fig. 2C and D). These findings suggest that corylin may exert its anticancer effects by downregulating c-Myc and its associated downstream signaling pathways.

Corylin induces G1 cell cycle arrest in OSCC cells

c-Myc is known to regulate cell cycle progression by modulating the expression of key cell cycle checkpoint regulators, including p21, cyclin D1, and CDK4.[24] To determine the effects of corylin on cell cycle distribution, flow cytometry was performed. The results revealed that corylin-treated OSCC cells exhibited a significant accumulation in the G1 phase, indicating G1 phase cell cycle arrest (Fig. 3A and B). Additionally, apoptotic cell populations were markedly increased compared to the control group (Fig. 3C—E). To further elucidate the underlying molecular mechanisms, Western blot analysis was conducted. The results demonstrated that corylin upregulated p21 expression, while CDC25A, cyclin D1, and CDK4 levels were downregulated, supporting the role of corylin in cell cycle arrest. Furthermore, corylin treatment downregulated Bcl-2 expression, confirming its ability to induce apoptosis in OSCC cells (Fig. 3F and G).

Corylin inhibits EMT in OSCC cells

Epithelial-mesenchymal transition (EMT) is a critical process that facilitates tumor invasion and metastasis. Previous studies have shown that c-Myc promotes EMT by upregulating vimentin, snail, and slug, thereby enhancing cancer cell migration and invasion.[25,26] To determine whether corylin affects EMT, OSCC cells were treated with different concentrations of corylin, and Western blot analysis was performed to assess EMT-related protein expression. The results revealed that N-cadherin, vimentin, and snail were significantly downregulated in corylin-treated cells, indicating that corylin effectively suppresses EMT and inhibits OSCC cell metastatic potential (Fig. 4).

Corylin enhances the anticancer effects of cisplatin and 5-FU in OSCC cells

To evaluate the potential of corylin in combination therapy, we investigated its synergistic effects with the chemotherapeutic agent cisplatin and 5-fluorouracil (5-FU). OSCC cells were treated with corylin alone, cisplatin alone, 5-FU alone, or a combination of both, and flow cytometry analysis was performed to assess cell viability and apoptosis. The results demonstrated that corylin significantly enhanced the cytotoxic effects of cisplatin and 5-FU. Compared to monotherapy with corylin or cisplatin/5-FU, the combination treatment significantly increased apoptosis induction, with a 104 % greater cytotoxic effect than single-agent treatments (Fig. 5A and B). Furthermore, DiOC6 staining confirmed that corylin and cisplatin/5-FU co-treatment led to enhanced cancer cell apoptosis compared to either agent alone (Fig. 5C and D). These findings suggest that corylin exerts a synergistic effect when combined with cisplatin and 5-FU, enhancing its anticancer activity and improving therapeutic efficacy in OSCC.

Discussion

Oral squamous cell carcinoma (OSCC) remains a highly aggressive malignancy with limited therapeutic options and poor prognosis, particularly due to high metastatic potential, recurrence, and resistance to chemotherapy. The oncogenic transcription factor c-Myc plays a pivotal role in

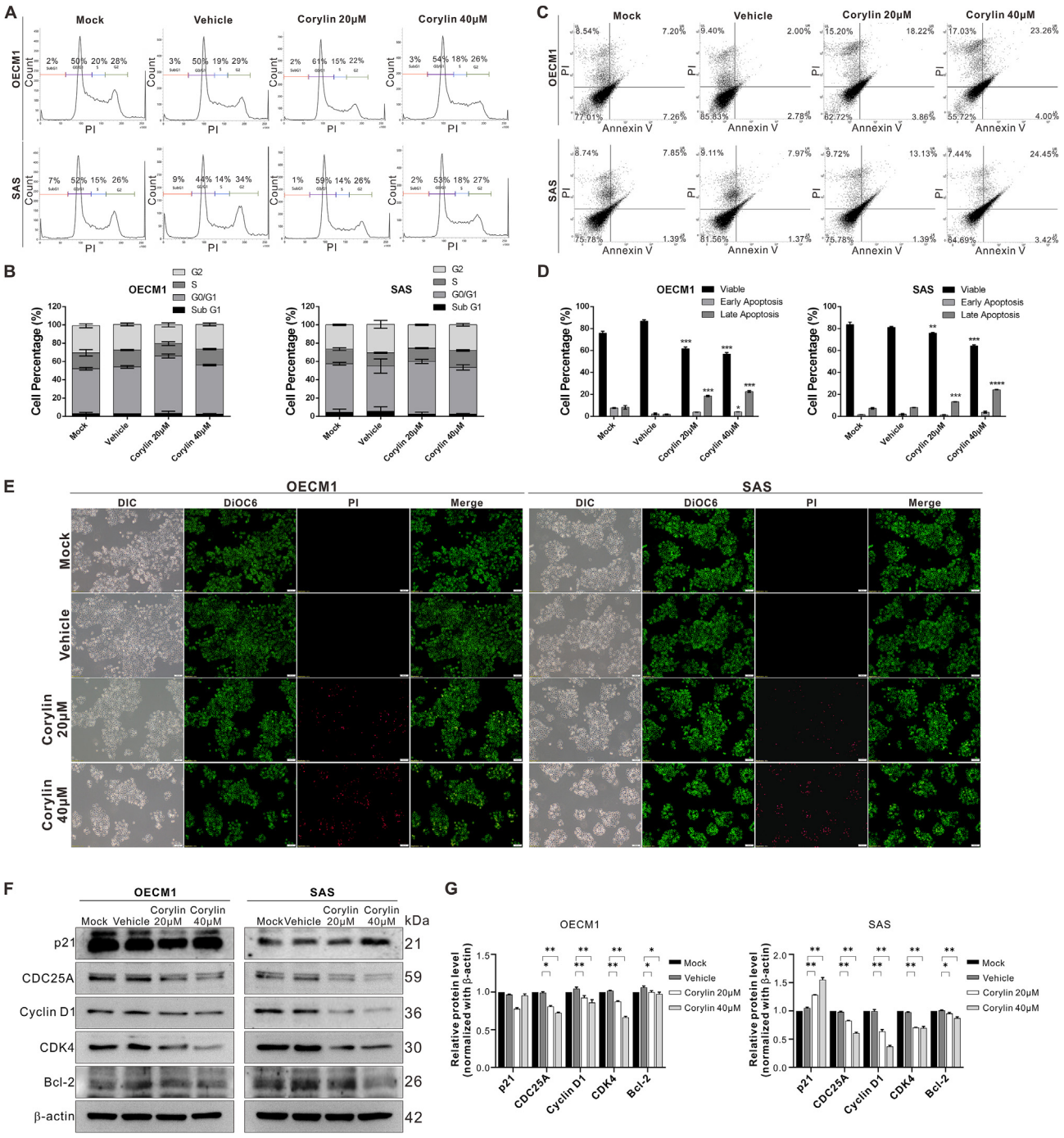

Figure 3 Corylin induces G1 phase arrest and promotes apoptosis in OSCC cells. (A, C) Flow cytometric analysis of cell cycle distribution and apoptotic rates in OSCC cells treated with 20 or 40 μM corylin for 24 h. (B, D) Quantification of cell populations in each phase of the cell cycle and apoptotic cells. (E) DiOC6/PI double staining to detect apoptotic cells. DIC: differential interference contrast. (F) Western blot analysis of key regulators of the cell cycle. (G) Quantification of protein expression levels. All experiments were conducted with three independent biological replicates. Results are presented as mean ± SD, with statistical significance determined by Student's t-test. Significance versus vehicle control: $P < 0.05$ (*), $P < 0.01$ (**).

OSCC progression by promoting uncontrolled proliferation, invasion, epithelial–mesenchymal transition (EMT), and drug resistance.[27] Since the lack of effective c-Myc-targeting therapies, natural compounds with potential c-Myc inhibitory activity are of significant interest in cancer treatment. In this study, we provide the first evidence that corylin, a flavonoid derived from Psoralea corylifolia, exerts potent anticancer effects in OSCC by downregulating c-Myc expression and its downstream signaling pathways (Fig. 5E). Our findings demonstrate that corylin significantly inhibits OSCC cell proliferation, migration, and invasion in a dose-dependent manner. Notably, the selectivity of corylin

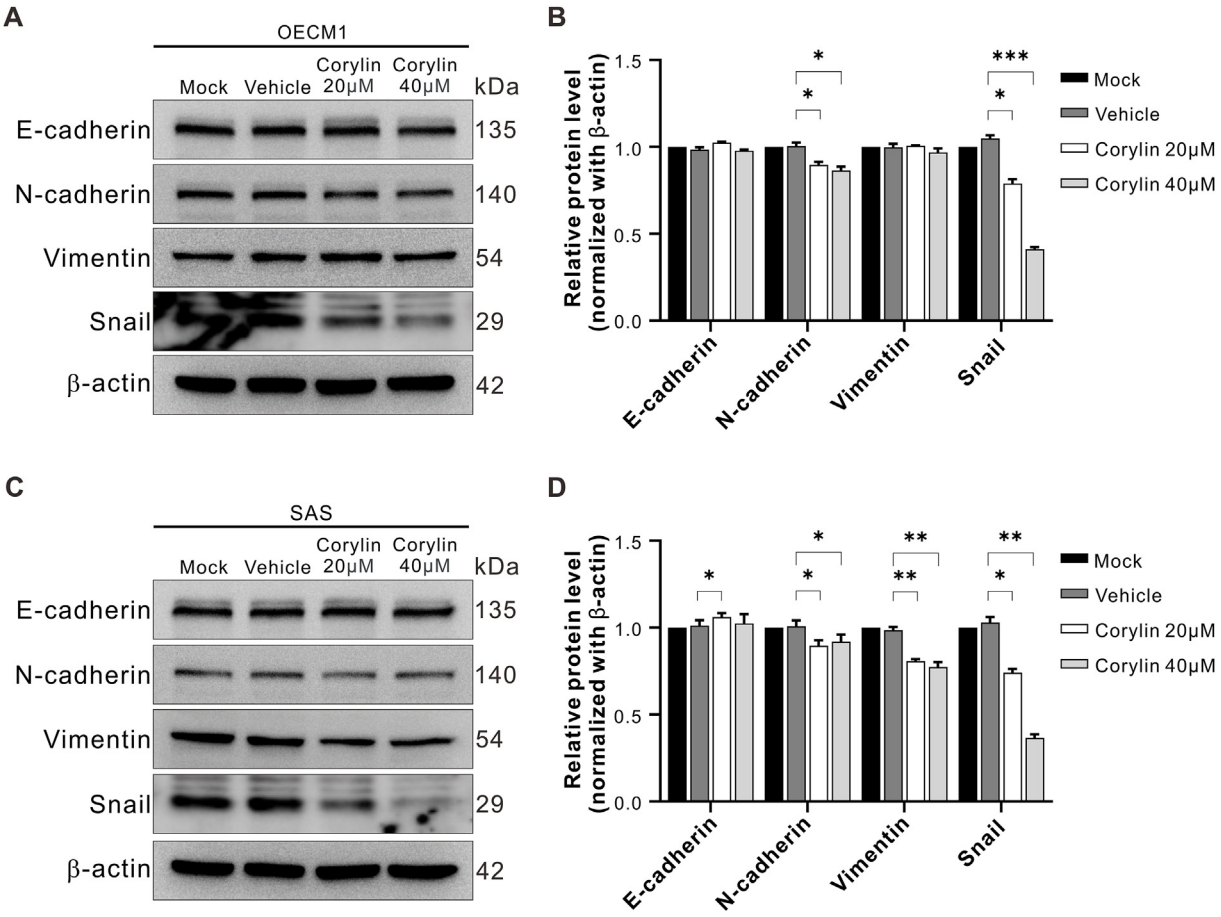

Figure 4 Corylin inhibits epithelial—mesenchymal transition (EMT) to suppress OSCC cell motility. (A, C) Western blot analysis of EMT-associated markers in OSCC cells treated with corylin. (B, D) Quantitative analysis of protein expression from three independent experiments. Results are presented as mean ± SD, with statistical significance determined by Student's t-test. Significant differences versus vehicle control: $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***).

was confirmed by its minimal cytotoxicity toward normal fibroblast cells, suggesting that corylin exerts preferential toxicity toward cancer cells. This selective activity is a crucial advantage over conventional chemotherapeutics, which often exhibit dose-limiting toxicities due to nonspecific cytotoxic effects on normal tissues.

Mechanistically, corylin-mediated c-Myc downregulation emerged as a key event in its anticancer activity. c-Myc overexpression is a hallmark of OSCC and numerous malignancies, where it facilitates tumor growth, therapy resistance, and metabolic reprogramming.[10,11,13] The observed suppression of c-Myc upon corylin treatment suggests that corylin directly or indirectly interferes with c-Myc transcription, stability, or degradation. Future studies should elucidate whether corylin exerts post-translational modifications to accelerate c-Myc turnover.

Uncontrolled proliferation is a defining characteristic of cancer, often driven by dysregulated cell cycle progression. Our results indicate that corylin induces G1-phase cell cycle arrest in OSCC cells, as evidenced by upregulation of p21 and downregulation of cyclin D1/CDK4, key regulators of G1-S phase transition. Since c-Myc is a crucial regulator of the G1-S checkpoint, its suppression by corylin likely contributes to the observed cell cycle blockade. Furthermore, corylin significantly enhances apoptosis, as indicated by the suppression of the anti-apoptotic protein Bcl-2. Given that OSCC cells often evade apoptosis via dysregulated c-Myc signaling, corylin-mediated c-Myc suppression represents a plausible mechanism for restoring apoptotic sensitivity. This suggests that corylin may be particularly effective in OSCC cases with high c-Myc expression, warranting further investigation into its efficacy in c-Myc-driven OSCC subtypes.

EMT plays a critical role in tumor invasion, metastasis, and resistance to therapy, allowing epithelial cancer cells to acquire mesenchymal-like properties that enhance motility and invasiveness. Previous studies have established c-Myc as a key regulator of EMT, where it induces the expression of EMT transcription factors (Snail, Slug, Twist) and mesenchymal markers (N-cadherin, vimentin).[25,27] Our findings indicate that corylin effectively suppresses EMT in OSCC cells, as evidenced by the downregulation of EMT markers upon corylin treatment. Since EMT is a major contributor to tumor recurrence and chemoresistance, the ability of corylin to revert EMT phenotypes suggests its potential as an anti-metastatic agent. Further in vivo studies using OSCC xenograft and metastasis models will be critical to determine whether corylin can effectively inhibit tumor dissemination in a physiological environment.

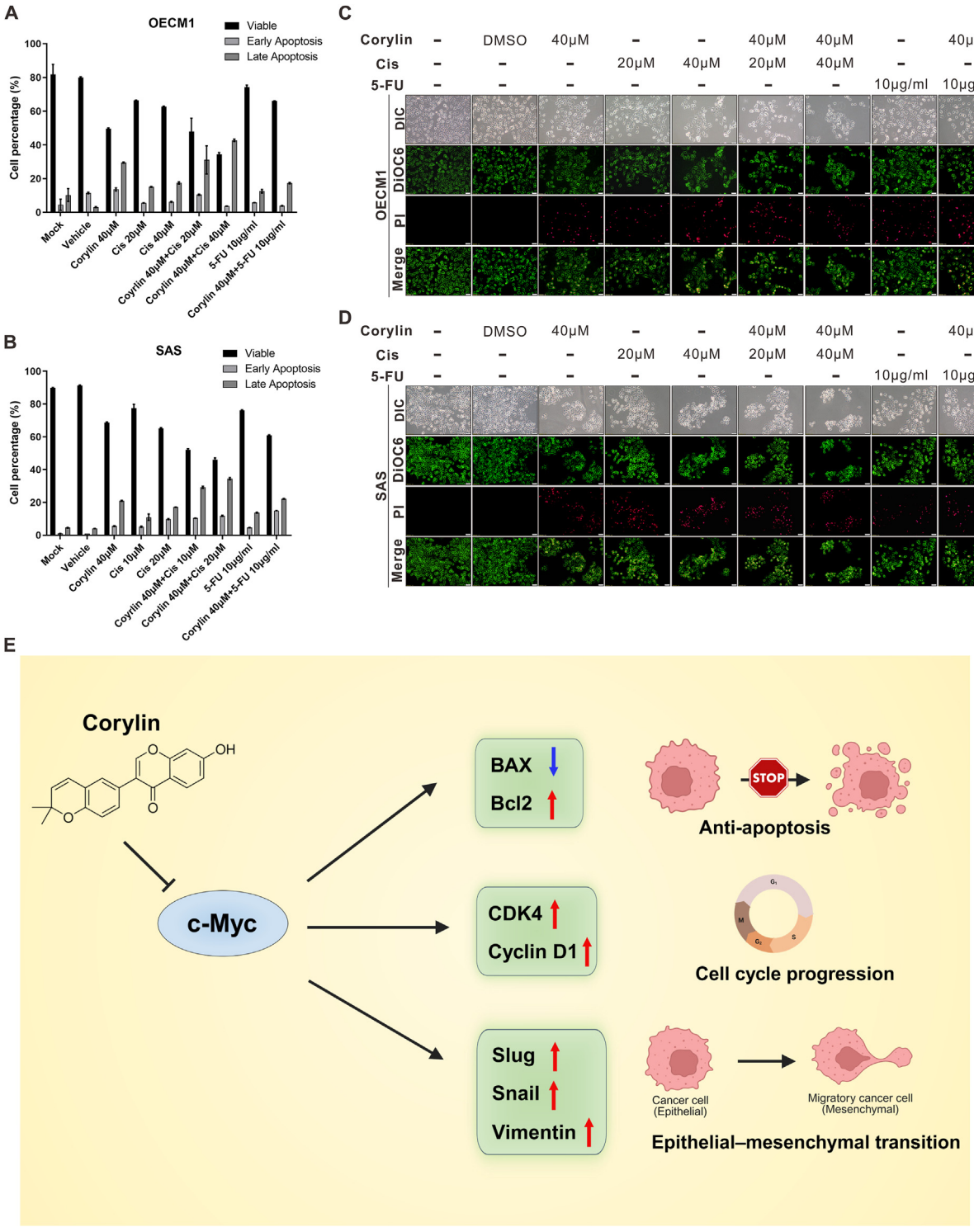

Figure 5 Corylin enhances the cytotoxic effects of cisplatin and 5-FU in OSCC cells. (A, B) Flow cytometric assessment of OSCC cell viability following 24-h treatment with corylin alone or in combination with cisplatin (Cis) or 5-FU. (C, D) DiOC6/PI staining confirms enhanced OSCC cell death with combination treatment. All experiments were conducted with three independent biological replicates. Data are shown as mean ± SD. DIC: differential interference contrast. (E) Schematic illustration summarizing the proposed anti-OSCC mechanisms of corylin (created with BioRender.com, accessed January 2024).

Cisplatin and 5-FU remains a standard chemotherapy for OSCC; however, its effectiveness is often limited by the rapid development of resistance, which is closely linked to c-Myc-driven survival pathways, EMT activation, and apoptosis evasion.[28,29] Our study shows that corylin markedly potentiates the cytotoxic effects of cisplatin and 5-FU,

leading to approximately a twofold increase in apoptosis compared to treatment with either agent alone. These results suggest that corylin sensitizes OSCC cells to cisplatin and 5-FU by targeting c-Myc-mediated resistance mechanisms, including EMT inhibition and apoptosis restoration. The synergistic effect of corylin and cisplatin/5-FU suggests that corylin may function as an adjuvant therapy, allowing for dose reduction of cisplatin and 5-FU while maintaining therapeutic efficacy. This has significant clinical implications, as lower cisplatin and 5-FU doses could help reduce treatment-associated toxicity (e.g., nephrotoxicity, neurotoxicity) while improving patient outcomes. Further studies in OSCC patient-derived xenografts (PDXs) and clinical samples will be necessary to determine the optimal combinatory treatment regimen.

Beyond OSCC, c-Myc is aberrantly activated in multiple cancers, including breast, lung, colorectal, and hepatocellular carcinoma.[11,25,26] Given that corylin effectively suppresses c-Myc expression and its downstream oncogenic pathways, it may exhibit therapeutic potential beyond OSCC, particularly in c-Myc-driven malignancies. Future research should assess corylin's anticancer activity in a broader spectrum of cancers and determine whether its mechanism of action extends across different tumor types. Additionally, emerging studies indicate that c-Myc plays a key role in regulating immune evasion by modulating immune checkpoint pathways and tumor-associated macrophages (TAMs).[27] Given this, corylin may also impact the tumor immune microenvironment, enhancing anti-tumor immune responses. Future studies should evaluate its effects on immune cell infiltration and inflammatory signaling within the tumor microenvironment.

The concentrations of corylin used in this study (20—40 μM) were determined based on dose—response analyses, which demonstrated robust anticancer activity in OSCC cells while exhibiting minimal cytotoxicity toward normal human fibroblasts. These findings suggest that corylin possesses a favorable therapeutic index in vitro. Although pharmacokinetic data for corylin are currently limited, evidence from related flavonoid compounds indicates that micromolar plasma concentrations may be achievable through oral administration or formulation-enhanced delivery systems.[30] To assess the clinical relevance of these in vitro concentrations, future studies should focus on characterizing the pharmacokinetic profile of corylin, including its bioavailability and tissue distribution. In addition, comprehensive in vivo toxicity profiling, including organ-specific assessments, will be essential to evaluate the safety and translational feasibility of corylin for clinical application.

In conclusion, this study provides compelling evidence that corylin exerts potent anticancer effects in OSCC by suppressing c-Myc expression, leading to G1-phase cell cycle arrest, EMT inhibition, and apoptosis induction. Additionally, corylin synergistically enhances cisplatin and 5-FU cytotoxicity, highlighting its potential as an adjuvant therapy to improve OSCC treatment outcomes. Given its selectivity for cancer cells and its ability to overcome key resistance mechanisms, corylin represents a promising therapeutic candidate for OSCC and other c-Myc-driven malignancies.

Declaration of competing interest

The authors declare no competing financial interests or personal relationships that could have influenced the work presented in this study.

Acknowledgments

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