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ORIGINAL RESEARCH

Synergistic Effects of Morin and Doxorubicin Overcome Chemoresistance in Ovarian Cancer: Preclinical Insights From in vitro and in vivo Models

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Background: Epithelial ovarian cancer (EOC) remains highly lethal due to late-stage diagnosis and chemoresistance, necessitating strategies to enhance conventional therapies like doxorubicin (DOX) while mitigating toxicity. This study evaluated morin, a flavonoid, as an adjunct to DOX in chemoresistant EOC models.

Methods: In vitro, DOX-resistant OVCAR-3-DR, OVCAR-3, and A2780 cells were treated with DOX, morin, or their combination. Synergy was assessed via MTT and apoptosis assays, alongside autophagy and cell cycle markers. In vivo, OVCAR-3-DR xenograft mice were divided into Sham, DOX (5 mg/kg), morin (15 and 30 mg/Kg), and combination groups. Tumor volume, apoptosis (BCL-2, caspase-3/9), autophagy (LC3, ATG5, Beclin-1), cell cycle regulators (Cyclin A2/D1), and oxidative stress (SOD, CAT, GPx, GR, GSH, MDA) were analyzed.

Results: Findings demonstrated significant synergistic cytotoxicity, with a combination index (CI) of 0.72, and enhanced apoptosis. Combination therapy suppressed Cyclin A2/D1, upregulated autophagy markers (, and reduced oxidative stress. In vivo, DOX +Morin30 reduced tumor volume synergistically ($p<0.001$) without systemic toxicity (stable body weight).

Conclusion: Morin synergizes with DOX by modulating apoptosis, autophagy, cell cycle, and oxidative stress, overcoming chemoresistance while reducing toxicity. These findings position morin as a promising, orally bioavailable adjunct worthy of further clinical investigation for optimizing DOX therapy in refractory EOC.

Keywords: ovarian neoplasms, flavonoids, drug resistance, apoptosis, autophagy, xenograft model antitumor assays

Introduction

Epithelial ovarian cancer (EOC) represents the predominant form of ovarian malignancy, constituting over 90% of cases, and remains the deadliest gynecological cancer in developed nations. Its high mortality rate is primarily due to advanced or metastatic-stage diagnosis and frequent recurrence.[1] EOC encompasses multiple histological subtypes, including high-grade serous carcinoma (approximately 70%), endometrioid and clear-cell carcinomas (each ~10%), mucinous tumors (~3%), and the less common low-grade serous variants.[2] Its insidious onset and vague symptomatology, such as bloating, pelvic discomfort, gastrointestinal disturbances, and fatigue, coupled with the absence of reliable early detection tools, result in more than 70% of diagnoses occurring at stage III or IV.[3,4] The causes of EOC are complex and involve genetics, hormones, lifestyle, and chronic inflammation.[5,6] Furthermore, the tumor microenvironment (TME) plays a critical role in disease progression and therapeutic outcome, with specific TME-associated gene signatures holding significant prognostic value.[7] At the molecular level, most cases typically have TP53 mutations, defects in homologous recombination, and activated survival pathways like PI3K/AKT/mTOR and NF-κB.[8–10] Other cases commonly feature mutations in RAS/MAPK and PI3K/AKT pathways, loss of tumor suppressors, and subtype-specific changes.[11,12] Autophagy in EOC has a dual role: initially, tumor-suppressive, but later aids tumor survival under stress.[13,14]

Current EOC treatment relies on maximal cytoreductive surgery followed by platinum-based chemotherapy, often combined with maintenance agents such as PARP inhibitors (eg, olaparib) and anti-angiogenic drugs (eg, bevacizumab).

https://doi.org/10.2147/CMAR.S567591
Received: 14 September 2025
Accepted: 16 December 2025
Published: 8 January 2026

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Despite improvements in systemic therapy, conventional regimens like platinum and taxanes are limited by resistance mechanisms, systemic side effects, and declining quality of life.[4,15,16] In the context of platinum-resistant or recurrent disease, doxorubicin (DOX) remains an option, showing modest response rates. DOX, an anthracycline antibiotic, exerts its cytotoxic effects by intercalating DNA and generating reactive oxygen species,[5] thereby inducing apoptosis. However, its clinical use is restricted by cumulative cytotoxicity, myelosuppression, and drug resistance.[17,18] Given these challenges, there is increasing interest in identifying safe, orally available agents that can potentiate the efficacy of conventional chemotherapies while mitigating toxicity. Phytochemicals, natural compounds with multi-targeted actions and favorable safety profiles, have gained traction in this context.[19] One such compound is morin (3, 5, 7, 2′, 4′-pentahydroxyflavone), a flavonoid found in various fruits, vegetables, and herbs.[20] Morin has demonstrated broad anticancer activities, including antioxidant, anti-inflammatory, and antiproliferative effects. Notably, morin has demonstrated favorable oral bioavailability in preclinical models, with studies reporting its absorption, distribution, and detection of active metabolites in plasma and tissues following oral administration, along with evidence that morin can enhance the bioavailability of co-administered chemotherapeutics.[20–22] Mechanistically, it promotes apoptosis through BCL-2 inhibition and caspase activation, modulates autophagy via LC3-II and Beclin-1 regulation, and counters oxidative stress by enhancing endogenous antioxidant systems.[23–26]

Accordingly, the present study was designed to evaluate whether oral administration of morin could potentiate the antitumor efficacy of doxorubicin in a xenograft mouse model of EOC. By analyzing biomarkers of apoptosis (BCL-2, caspase-3, caspase-9), autophagy (LC3, ATG5, Beclin-1), cell cycle progression (Cyclin A, Cyclin D1), and oxidative stress (SOD, CAT, GSH, ROS, GPx, MDA), the study aimed to elucidate the underlying molecular mechanisms driving any observed synergistic effects.

Materials and Methods

Cell and Chemicals

Human ovarian cancer cell lines A2780 and OVCAR-3 were obtained from the American Type Culture Collection (ATCC) and AcceGen, respectively. Doxorubicin hydrochloride (DOX, ≥98% purity) and morin (MRN, ≥98% purity) were purchased from Sigma-Aldrich. Additional reagents, including 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), and a protease and phosphatase inhibitor cocktail, were also sourced from Sigma (St. Louis, MO, USA). Culture media and supplements, including fetal bovine serum (FBS), RPMI-1640, penicillin-streptomycin, and amphotericin B, were supplied by Gibco-BRL (Grand Island, NY, USA). A protein extraction kit was obtained from Abcam (USA). Enzyme-linked immunosorbent assay kits were used to quantify key proteins: LC3 (MyBioSource, Cat. #MBS1603826), Cyclin A2 (MyBioSource, Cat. #MBS8804448), Cyclin D1 (Abcam, Cat. #ab214571), ATG5 (MyBioSource, Cat. #MBS2602759), and Beclin1 (MyBioSource, Cat. #MBS732891). Moreover, colorimetric assay kits for evaluating antioxidant and oxidative stress markers SOD, CAT, GPx, GSH, and MDA were purchased from R&D Systems and Biocompare.

Establishment of Doxorubicin-Resistant Ovarian Cancer Cell Line

To develop the DOX-resistant OVCAR-3 cell line (OVCAR-3-DR cell line), parental OVCAR-3 cells were subjected to gradually increasing concentrations of DOX. The induction process began with a 0.1 μM DOX treatment for two weeks. Surviving cells were then allowed to recover in drug-free medium before being exposed to escalating DOX concentrations, 0.25, 0.5, 1, and finally 2 μM, each for a duration of two weeks. This stepwise selection continued until cells exhibited a stable resistance phenotype, defined by an IC_{50} of 2 μM or higher. The resistant population was subsequently maintained in culture medium containing 2 μM DOX and allowed to grow in drug-free conditions for at least one week prior to experimentation. All cells were cultured in RPMI-1640 medium supplemented with 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin.

In Vitro Cytotoxicity Assay (MTT)

In vitro cytotoxicity was evaluated by MTT assay on OVCAR-3, OVCAR-3-DR, and A2780 cells. Briefly, 8×10^3 cells per well were plated in 96-well plates and allowed to adhere for 24 h at 37 °C in a humidified atmosphere containing 5% CO_2. Cells were then exposed for 24 h to a range of concentrations of doxorubicin (0.1, 0.5, 1, 2 and 5 μM), morin (10, 25, 50, 75 and 100 μM). Following treatment, 20 μL of 5 mg/mL MTT solution was added to each well and incubated for 4 h to allow formazan crystal formation. Crystals were dissolved in 150 μL DMSO, and the absorbance at 570 nm was recorded with a microplate reader. Cell viability was calculated relative to untreated controls, and IC_{50} values were derived using GraphPad Prism. Synergistic interactions were assessed by calculating the combination index via the Chou–Talalay method in CompuSyn software.

In Vitro Apoptosis Assay by PI/Annexin V Staining

Apoptotic cell death was quantified by flow cytometry using the Annexin V-FITC/Propidium Iodide Apoptosis Detection Kit (BD Biosciences). Cells were exposed for 24 hours to doxorubicin (1 μM), morin (50 μM), or their combination (1 μM DOX + 50 μM morin), based on previously determined in vitro IC_{50} values. After treatment, cells were harvested, washed twice with ice-cold PBS, and resuspended in binding buffer. They were then stained with 5 μL Annexin V-FITC and 5 μL PI for 15 minutes at room temperature in the dark. Stained samples were analyzed on a BD FACSCanto II flow cytometer, and FlowJo software was used to distinguish early apoptotic (Annexin V+/PI^-) from late apoptotic (Annexin V+/PI+) populations.

Animal Care, Xenograft Development, and Experimental Protocol

Female athymic BALB/c nude mice, aged 6 to 8 weeks and weighing between 18–22 g, were procured from the university's accredited animal facility. The animals were maintained under specific-pathogen-free conditions, with controlled environmental parameters including a temperature of 22 ± 3°C, relative humidity of 50 ± 5%, and a 12-hour light/dark cycle. Animals were provided unrestricted access to standard food and water and acclimatized for one week prior to the initiation of experiments.

OVCAR-3-DR cells were collected at 70–80% confluence, rinsed twice with ice-cold phosphate-buffered saline (PBS), and resuspended at a concentration of 1×10^7 cells/mL in a 1:1 mixture of PBS and growth factor-reduced Matrigel. To induce peritoneal tumors, each mouse received an intraperitoneal injection of 100 μL of the cell suspension, equivalent to 1×10^6 cells. Fourteen days post-inoculation, successful tumor engraftment was verified through abdominal palpation and bioluminescent imaging following intraperitoneal injection of D-luciferin (150 mg/kg). Subsequently, mice were randomly allocated into six treatment groups (n = 8 per group) using a computer-generated randomization schedule to ensure unbiased group distribution, including: (1) Sham (intraperitoneal 0.9% sterile NaCl and oral 0.5% carboxymethyl cellulose (CMC)); (2) Doxorubicin (DOX) alone (5 mg/kg intraperitoneally every 3 days); (3) MOR15 (morin 15 mg/kg, administered orally once daily); (4) MOR30 (morin 30 mg/kg, orally once daily); (5) DOX combined with MOR15; (6) DOX combined with MOR30. The present sample size was chosen considering parameters such as statistical power and reliability (8 animals in each group provides sufficient statistical power to detect significant differences between studied groups while accounting for biological variability in tumor growth and treatment response), ethical compliance, experimental design complexity (48 animals in 6 studied groups balances logistical feasibility with robust group comparisons), and based on the prior ovarian cancer xenograft studies.

The dosing regimens were selected based on the following rationale. The dose of doxorubicin (5 mg/kg) is a well-characterized, sub-maximal dose in murine models that allows for the clear observation of combinatory effects. The doses of morin (15 and 30 mg/kg) were chosen from the existing literature demonstrating its oral bioavailability and efficacy in preclinical models. The combination of these agents was directly informed by the robust synergistic interaction (CI = 0.72) observed at the 1:50 (DOX:Morin) ratio in our in vitro studies. Throughout the treatment period and during a subsequent three-week follow-up, mice were monitored for general health and body condition. On day 22, animals were euthanized by CO_2 inhalation; peritoneal tumors were excised, weighed, and measured. Tumor volume measurements and subsequent molecular analyses were performed by researchers blinded to the group allocations to

prevent observer bias. Tumor volume was calculated using the formula:

$$Tumor\ Volume = ((Length) \times (Width)^2)/2$$

Excised tumors were immediately snap-frozen in liquid nitrogen for downstream molecular analyses.

Real-Time Quantitative Polymerase Chain Reaction (qRT-PCR)

Tumor tissue was homogenized, and total RNA was isolated using the PureLink RNA Mini Kit (Thermo Fisher Scientific, USA; Catalog No. 12183018A) in accordance with the manufacturer's guidelines. RNA purity and concentration were evaluated spectrophotometrically using a BioTek NanoDrop system. Complementary DNA (cDNA) was synthesized from the extracted RNA using the High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, USA; Catalog No. 4368814). Quantitative PCR amplification was performed on a StepOne Real-Time PCR System (Applied Biosystems, USA) with Maxima SYBR Green qPCR Master Mix (Thermo Fisher Scientific, USA; Catalog No. K0253). Gene-specific primers (Table 1) were used to amplify target sequences under the following cycling conditions: initial denaturation at 95°C for 5 minutes, followed by 40 cycles of denaturation (95°C, 15 seconds), annealing (60°C, 15 seconds), and extension (72°C, 20 seconds). Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) served as the endogenous control for normalizing gene expression. Relative quantification of target transcripts was calculated using the $2^{-\Delta\Delta CT}$ method to determine fold changes in expression levels.

Enzyme-Linked Immunosorbent Assay

Frozen tumor tissue samples were homogenized in ice-cold RIPA lysis buffer containing protease and phosphatase inhibitors to preserve protein integrity. Total protein concentration was quantified using the Pierce™ BCA Protein Assay Kit. Subsequently, levels of cell cycle markers (Cyclin A and D1), apoptosis (BCL-2 levels, caspase-3 and caspase-9 activity), and autophagy-related proteins (LC3, ATG5, and Beclin-1) were analyzed using commercially available ELISA kits. All procedures were performed in strict accordance with the manufacturer's protocols to ensure reproducibility.

Table 1 Primer Sequences

Primer	Sequence
GAPDH forward	5′-GGTGGACCTCATGGCCTACAT-3′
GAPDH reverse	5′-GCCTCTCTCTTGCTCTCAGTATCCT-3′
CCND1 forward	5′-ATATTCCGTAGGTAGATGTGTAAC-3′
CCND1 reverse	5′-TGTCACTATTTCGTCTTCTC-3′
CCNA2 forward	5′-GTCACCACATACTATGGACATG-3′
CCNA2 reverse	5′-AAGTTTTCCTCTCAGCACTGAC-3′
BCL-2 forward	5′-CGACCTCTGTTTGATTTCTCCTG-3′
BCL-2 reverse	5′-CTTTTCATATTTGTTTGGGGC-3′
LC3 forward	5′-GGTCCAGTTGTGCCTTTATTGA-3′
LC3 reverse	5′-GTGTGTGGGTTGTGTACGTCG-3′
Beclin 1 forward	5′-CTGGACACTCAGCTCAACGTCA-3′
Beclin 1 reverse	5′-CTCTAGTGCCAGCTCCTTTAGC-3′
ATG5 forward	5′-TCAGCCACTGCAGAGGTGTTT-3′
ATG5 reverse	5′-GGCTGCAGATGGACAGTTGCA-3′

Protein concentrations for each target were calculated by interpolating absorbance data against a standard curve generated from known reference standards.

Assessment of Oxidative Stress Parameters

The enzymatic activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase in tumor tissue homogenates were evaluated using commercial colorimetric assay kits. Reduced glutathione (GSH) levels were quantified via the DTNB method, while malondialdehyde (MDA) concentrations were determined using the thiobarbituric acid reactive substances (TBARS) assay.

Statistical Analysis

Data are expressed as mean ± standard deviation. Data distribution and variance homogeneity were assessed before hypothesis testing. A statistical significance threshold was set at $p < 0.05$. One-way analysis of variance (ANOVA) was used, followed by Tukey's post-hoc test for multiple comparisons. Statistical analyses were carried out using SPSS software (version 24.0; IBM Corp., Chicago, IL, USA), and all graphical visualizations were created with GraphPad Prism (version 8.0; GraphPad Software, San Diego, CA, USA).

Results

Synergistic Cytotoxicity of Morin and DOX in Chemoresistant Ovarian Cancer Cells

MTT assays demonstrated dose-dependent cytotoxicity for Dox and morin in A2780, OVCAR-3, and doxorubicin-resistant OVCAR-3-DR cells (Figure 1). For Dox, the mean cell viability (±SD) at 5.0 μM was 21.3 ± 4.0% in A2780, 36.0 ± 3.4% in OVCAR-3, and 47.6 ± 4.5% in OVCAR-3-DR, confirming resistance in the latter two lines. Morin alone reduced viability at 100 μM to 21.1 ± 3.2% in A2780, 28.0 ± 5.6% in OVCAR-3, and 35.3 ± 2.3% in OVCAR-3-DR. IC_{50} values for Dox and morin in OVCAR-3-DR were calculated as 1.5 ± 0.2 μM and 60 ± 5.1 μM, respectively. Based on these values, a fixed ratio of 1:50 (Dox:Morin) was selected to evaluate combinatorial effects. This ratio utilized sub-IC_{50} doses (1 μM Dox and 50 μM Morin) to minimize toxicity while targeting resistance mechanisms. Synergy analysis via the Chou-Talalay method yielded a combination index (CI) of 0.72 ± 0.08, confirming significant synergistic interaction ($p < 0.05$).

Morin Potentiates DOX-Induced Apoptosis in Chemoresistant Ovarian Cancer Models

Flow cytometric analysis using Annexin V/PI staining revealed significant induction of apoptosis across all cell lines following treatment with Dox, morin, or their combination (Figure 2). In A2780 cells, Dox increased apoptosis to 40.12% ($p < 0.01$), while morin elevated apoptosis to 16.36% ($p < 0.05$). The combination of Dox and morin further enhanced apoptosis to 61.00% ($p < 0.001$), demonstrating a synergistic effect. Similarly, in OVCAR-3 cells, apoptosis rose to 5.27-fold with Dox and 2.37-fold with morin, reaching 8.87-fold ($p < 0.001$) with combined treatment. Notably, in doxorubicin-resistant OVCAR-3-DR cells, Dox alone induced only 2.85-fold ($p < 0.05$), whereas morin alone elicited a higher apoptotic response (5.35-fold, $p < 0.05$). The combination therapy significantly amplified apoptosis to 33.82% ($p < 0.001$), overcoming resistance observed with Dox monotherapy.

Combination Therapy Induces Cell Cycle Arrest via Cyclin A2 and D1 Suppression

Treatment with 1 μM Dox and 50 μM Morin alone or combined significantly reduced Cyclin A2 and Cyclin D1 levels in ovarian cancer cells (Figure 3). In sensitive A2780 cells, Cyclin A2 decreased by 24.7% with Dox ($p < 0.05$) and 34.4% with the combination ($p < 0.001$), while Cyclin D1 declined by 22.1% under combination therapy ($p < 0.01$). OVCAR-3 cells exhibited 23.7% ($p < 0.05$) and 35.6% ($p < 0.001$) reductions in Cyclin A2 with Dox and combination, respectively, and a 19.9% ($p < 0.05$) decrease in Cyclin D1 with the combination. In resistant OVCAR-3-DR cells, the combination reduced Cyclin A2 by 29.7% ($p < 0.001$) and Cyclin D1 by 35.6% ($p < 0.001$), overcoming resistance observed with Dox alone (Cyclin A2: 7.9%, $p > 0.05$; Cyclin D1: 2.3%, $p > 0.05$).

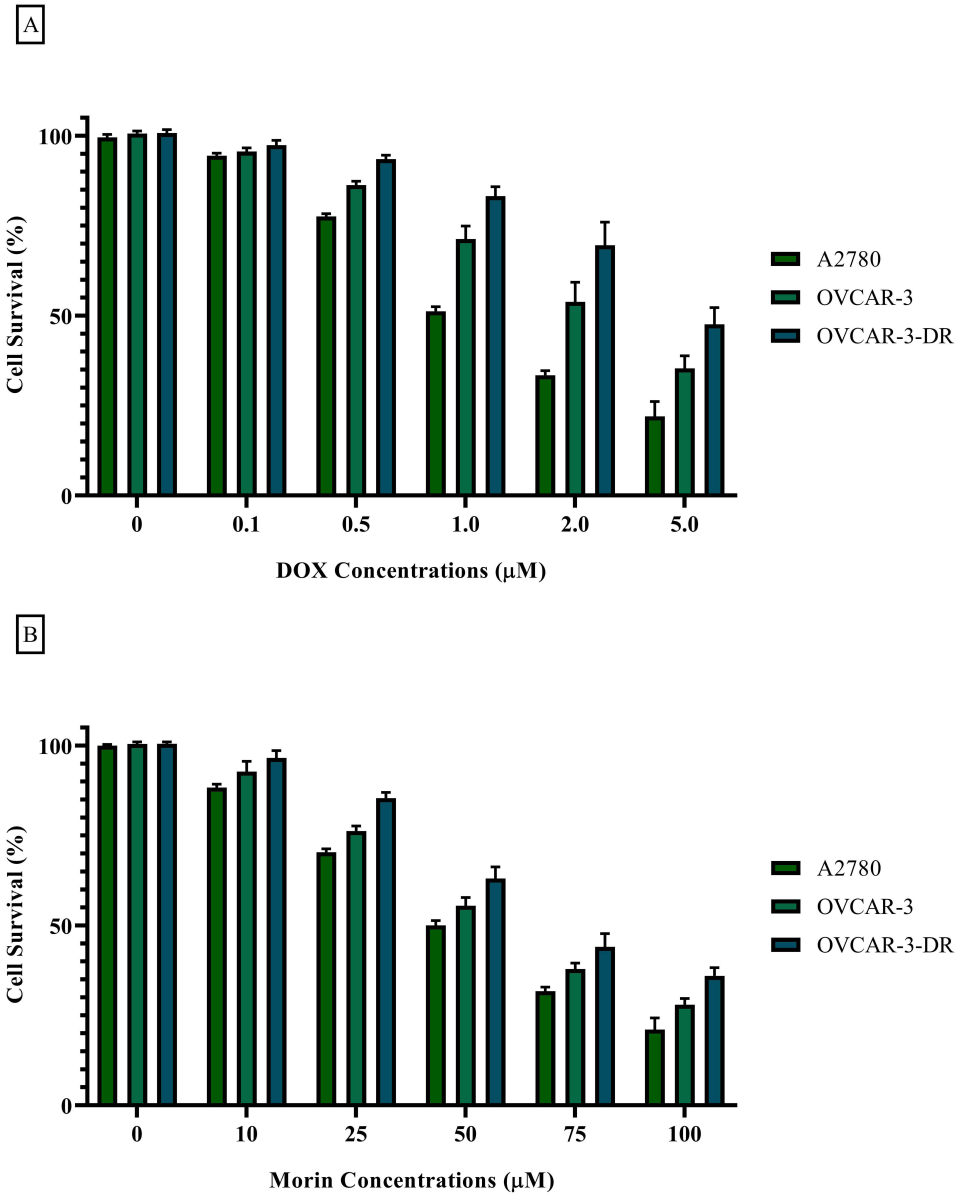

Figure 1 In vitro cytotoxicity of doxorubicin and morin in ovarian cancer cell lines. (**A**) Dose-dependent cytotoxicity of DOX (0.1–5 μM) and (**B**) morin (10–100 μM) in A2780, OVCAR-3, and doxorubicin-resistant OVCAR-3-DR cells, as measured by MTT assay. Data are presented as mean ± SD of n=6 biological replicates.

Morin Synergizes with DOX to Activate Autophagy in Chemoresistant Tumors

ELISA quantification revealed significant dose-dependent upregulation of autophagy-related proteins in A2780, OVCAR-3, and doxorubicin-resistant OVCAR-3-DR cells following treatment with Dox (1 μM), Morin (50 μM), or their combination (Figure 4). In A2780 cells, LC3 levels increased by 1.7-fold under combination therapy compared to control ($p < 0.001$), with similar trends observed for ATG5 ($p < 0.01$) and BECN-1 ($p < 0.001$). OVCAR-3 cells exhibited analogous responses, where combined treatment elevated LC3 (2.0-fold, $p < 0.001$), ATG5 (1.7-fold, $p < 0.01$), and BECN-1 (1.9-fold, $p < 0.001$) relative to untreated controls. Notably, in resistant OVCAR-3-DR cells, the combination regimen overcame drug resistance, increasing LC3 ($p < 0.05$), ATG5 (1.7-fold, $p < 0.01$), and BECN-1 ($p < 0.001$) more effectively than monotherapy ($p > 0.05$ vs Dox or Morin alone), indicating that morin synergizes with Dox to amplify autophagy activation, even in chemoresistant ovarian cancer cells.

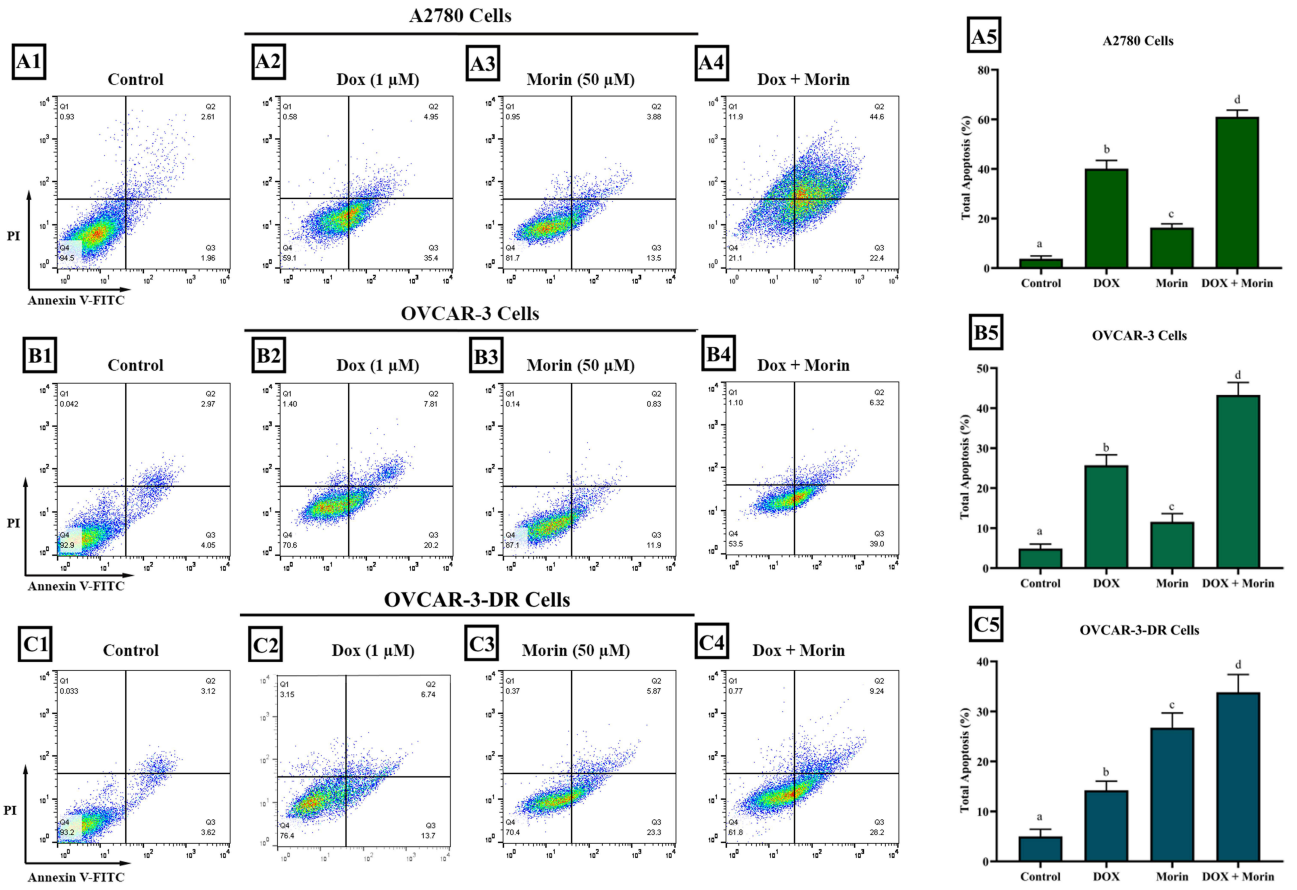

Figure 2 Apoptotic effects of doxorubicin and morin in ovarian cancer cells. Flow cytometry analysis (Annexin V/PI staining) showing apoptosis induction in (**A1**–**A5**) A2780, (**B1**–**B5**) OVCAR-3, and **(C1–C5**) OVCAR-3-DR cells treated with control, DOX (1 μM), morin (50 μM), or their combination. Data are presented as mean ± SD of n=6 biological replicates. Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. Bars not sharing a common lowercase letter (a, b, c, d) are significantly different from each other ($p < 0.05$).

Combination Therapy Attenuates Tumor Growth and Systemic Toxicity in Xenograft Models

The antitumor efficacy and systemic toxicity of morin, alone or in combination with Dox, were evaluated in OVCAR-3-DR xenograft mice (Figure 5). Tumor volume analysis demonstrated that Dox and morin monotherapy (MOR15 and MOR30 groups) caused a slight reduction in tumor growth compared to the Sham group ($p > 0.05$). Whereas the combination of Dox with MOR15 and MOR30 induced a striking synergistic reduction in tumor volume ($p < 0.001$ vs all groups). Body weight measurements revealed that Dox monotherapy caused mild weight loss compared to Sham animals ($p < 0.05$), while morin-treated groups and combination therapies maintained body weights comparable to Sham ($p > 0.05$), indicating minimal systemic toxicity.

Combination Therapy Elevated Apoptosis in Ovarian Cancer Xenografts

Quantification of apoptotic markers in tumor tissues revealed significant alterations in BCL-2 levels and caspase-3/caspase-9 activities across treatment groups (Figure 6). RT-qPCR analysis of *BCL-2* gene expression paralleled these trends. Sham tumors exhibited baseline *BCL-2* mRNA levels, DOX monotherapy induced a nonsignificant decrease ($p > 0.05$). MOR15 marginally reduced expression ($p > 0.05$), and similarly MOR30 elicited a non-significant downregulation ($p > 0.05$). The combination regimens exerted profound transcriptional suppression: DOX+MOR15 and DOX+MOR30 caused 15.17% decrease ($p < 0.01$) and 53.0% decrease ($p < 0.001$) in *BCL-2* mRNA, respectively. Additionally, BCL-2 protein levels were measured using ELISA. In the Sham group, BCL-2 levels averaged 19.7 ± 0.8 ng/mg protein,

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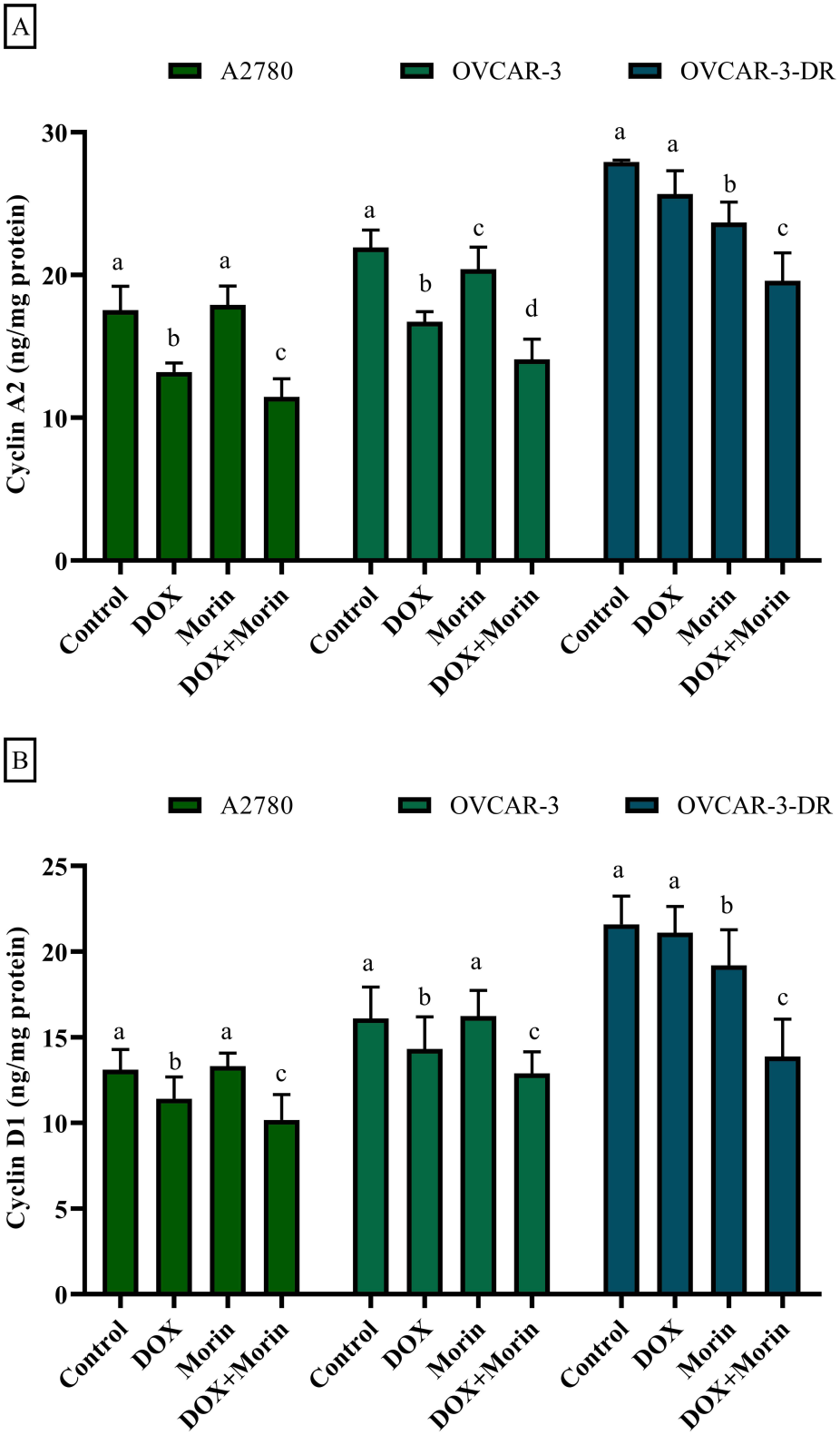

Figure 3 Modulation of cell cycle regulators by doxorubicin and morin. ELISA quantification of (**A**) Cyclin A2 and (**B**) Cyclin D1 protein levels in A2780, OVCAR-3, and OVCAR-3-DR cells after treatment with control, DOX (1 μM), morin (50 μM), or their combination. Data are presented as mean ± SD of n=6 biological replicates. Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. Within each cell line, bars not sharing a common lowercase letter (a, b, c, d) are significantly different from each other ($p < 0.05$).

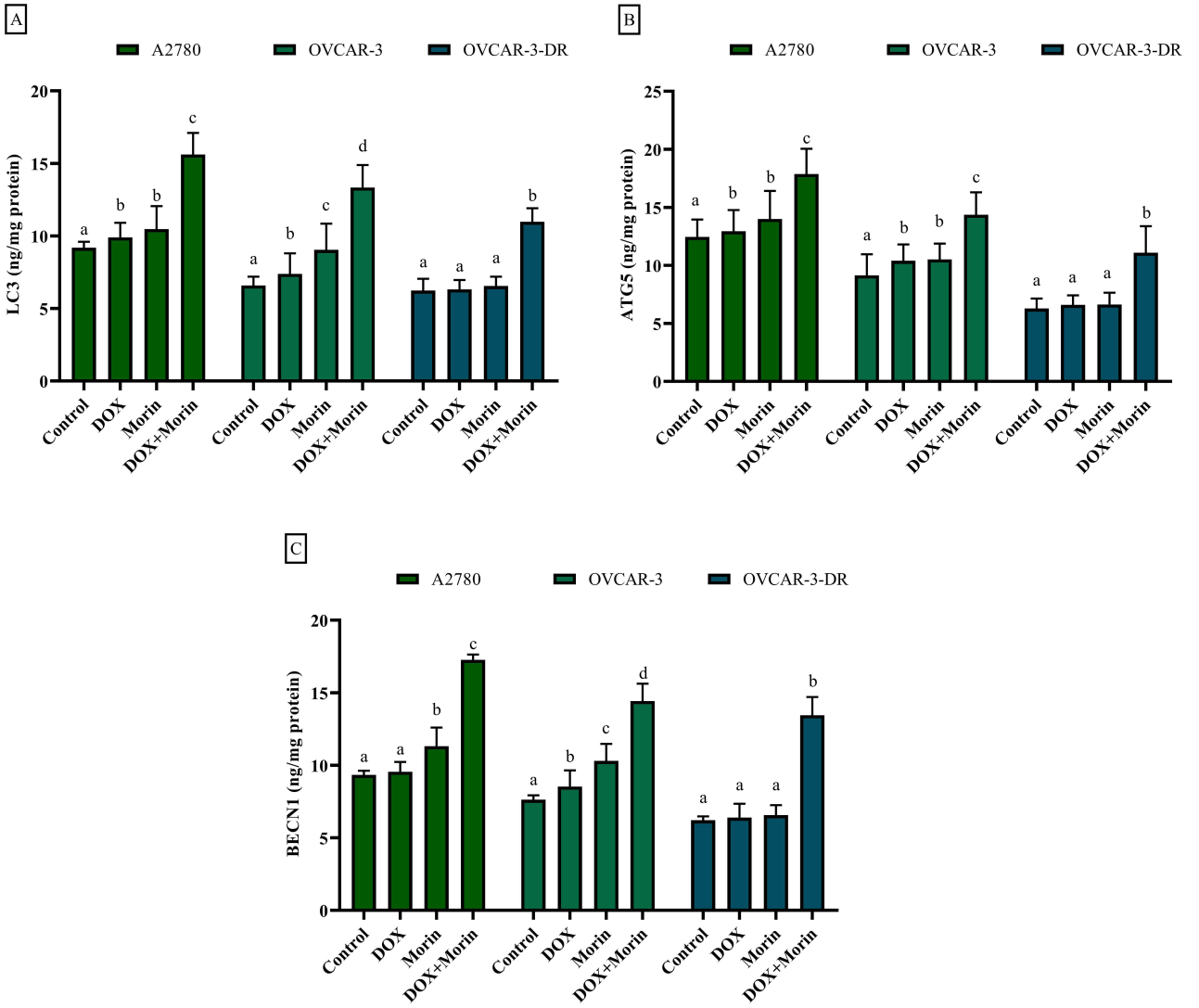

Figure 4 Autophagy activation by doxorubicin and morin in vitro. Dose-dependent upregulation of autophagy markers (**A**) LC3, (**B**) ATG5, and (**C**) BECN1 in A2780, OVCAR-3, and OVCAR-3-DR cells treated with control, DOX (1 μM), morin (50 μM), or their combination, as measured by ELISA. Data are presented as mean ± SD of n=6 biological replicates. Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. Within each cell line and for each marker, bars not sharing a common lowercase letter (a, b, c, d) are significantly different from each other ($p < 0.05$).

reflecting baseline anti-apoptotic signaling. DOX monotherapy modestly reduced BCL-2 to a mean of 18.8 ng/mg protein ($p > 0.05$ vs Sham), consistent with chemoresistance in the OVCAR-3-DR xenograft model. Morin monotherapy demonstrated dose-dependent efficacy: MOR15 caused a negligible reduction ($p > 0.05$), while MOR30 further suppressed levels to a 7.26% reduction ($p < 0.05$). Strikingly, combination therapies synergistically enhanced BCL-2 suppression, with DOX+MOR15 and DOX+MOR30 reducing levels to 37.33% ($p < 0.01$) and 67.30% ($p < 0.001$), respectively. Moreover, both groups demonstrated a significant reduction when compared to DOX animals ($p < 0.01$).

Caspase-3 and caspase-9 activities mirrored these apoptotic shifts. Sham animals showed baseline caspase-3 activity and caspase-9 activity. DOX monotherapy nonsignificantly elevated caspase-3 ($p > 0.05$) and caspase-9 ($p > 0.05$). MOR30 altered caspases activities as caused 1.36-fold ($p < 0.05$) and 1.67-fold ($p < 0.05$) increase in the activity of caspase-3 and caspase-9, respectively. Synergistic effects dominated in combination groups: DOX+MOR30 elevated caspase-3 (4.0-fold, $p < 0.001$) and caspase-9 (4.21-fold, $p < 0.001$) activities, surpassing all monotherapies ($p < 0.001$).

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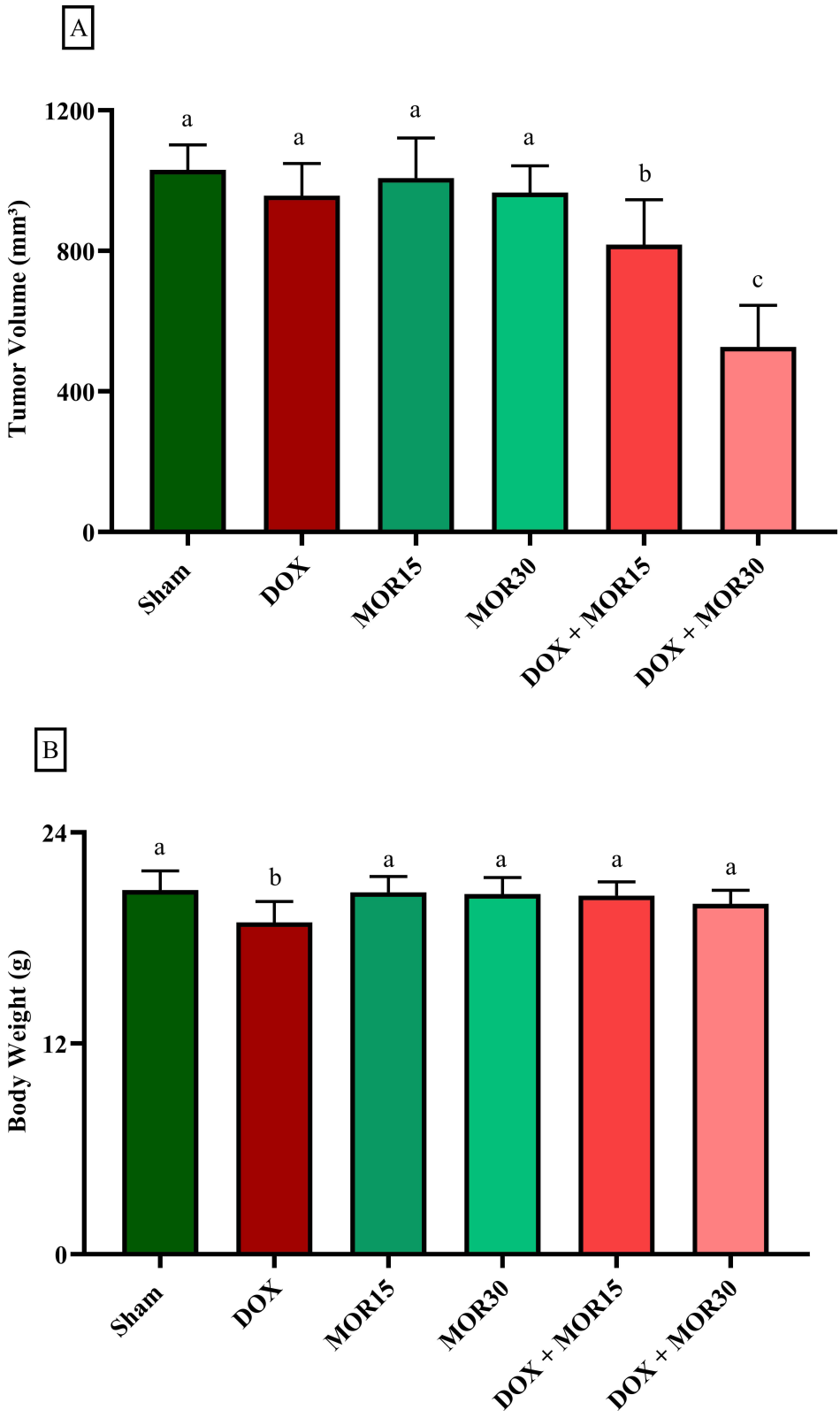

Figure 5 In vivo antitumor efficacy of combinatorial therapy. (**A**) Tumor volume and (**B**) total body weight measurements in OVCAR-3-DR xenograft mice treated with Sham, doxorubicin (DOX, 5 mg/kg), morin (MOR15 or MOR30 mg/Kg), or their combinations. Data are expressed as mean ± SD (n=8). Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. In (**A**), bars not sharing a common lowercase letter (a, b, c) are significantly different from each other ($p < 0.05$). In (**B**), no significant differences were found between the combination groups and the Sham group ($p > 0.05$).

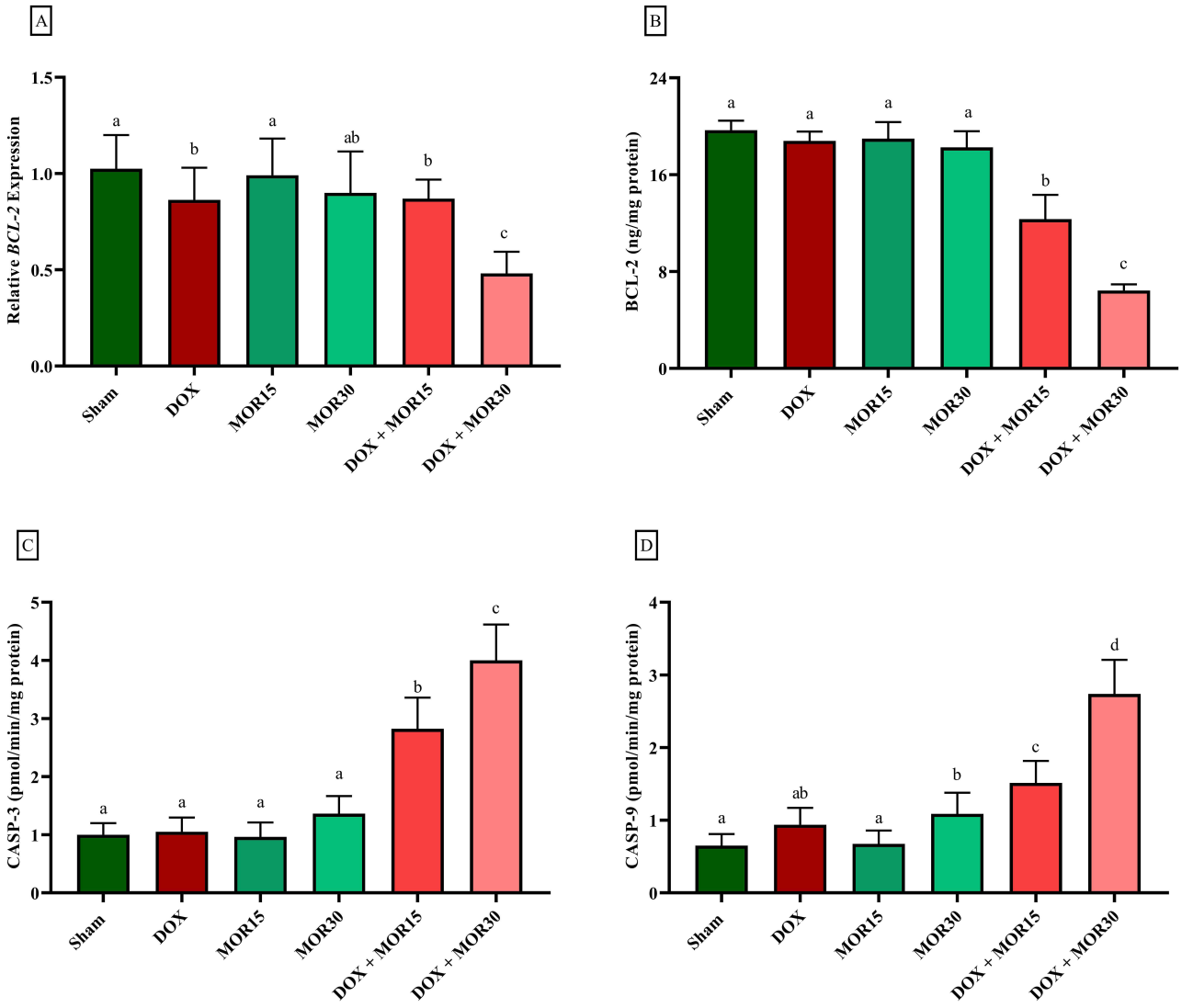

Figure 6 Apoptotic marker modulation in tumor tissues. (**A**) RT-qPCR analysis of *BCL-2* mRNA expression. (**B**) ELISA quantification of BCL-2 protein levels. Activity of (**C**) caspase-3 and (**D**) caspase-9 in xenograft tumors from the six treatment groups. Data are expressed as mean ± SD (n=8). Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. Bars not sharing a common lowercase letter (a, b, c, d) are significantly different from each other ($p < 0.05$).

Modulation of Cell Cycle Markers by DOX and Morin in Ovarian Cancer Xenografts

Quantification of cell cycle regulators in tumor tissues revealed significant alterations in cyclin A2 and cyclin D1 levels across treatment groups (Figure 7). RT-qPCR analysis of *CCNA2* and *CCND1* gene expression demonstrated dose-dependent suppression in combination therapy groups compared to monotherapy or Sham controls. Sham tumors exhibited baseline cyclin A2 levels, which remained largely unchanged following DOX monotherapy ($p > 0.05$). MOR15 and MOR30 monotherapy reduced cyclin A2 levels to 21.6 ± 0.9 ng/mg ($p > 0.05$) and 20.9 ± 1.1 ng/mg ($p > 0.05$), respectively. Strikingly, the combination of DOX with MOR15 ($p < 0.01$ vs Sham) and MOR30 ($p < 0.001$ vs all groups) synergistically suppressed cyclin A2 representing 10.3% and 20.8% reductions compared to Sham, respectively.

Similarly, Cyclin D1 levels in Sham tumors averaged 19.4 ± 0.7 ng/mg protein. DOX, MOR15, and MOR30 monotherapy induced a nonsignificant reduction ($p > 0.05$). The combination regimens exerted profound inhibitory effects: DOX+MOR15 decreased Cyclin D1 ($p < 0.01$ vs Sham), and DOX+MOR30 further suppressed levels corresponding to a 29.9% reduction compared to Sham ($p < 0.001$). These findings indicate that morin synergizes with DOX to potentiate cell cycle arrest, particularly at the higher dose (30 mg/kg), overcoming resistance observed with DOX alone.

https://doi.org/10.2147/CMAR.S567591

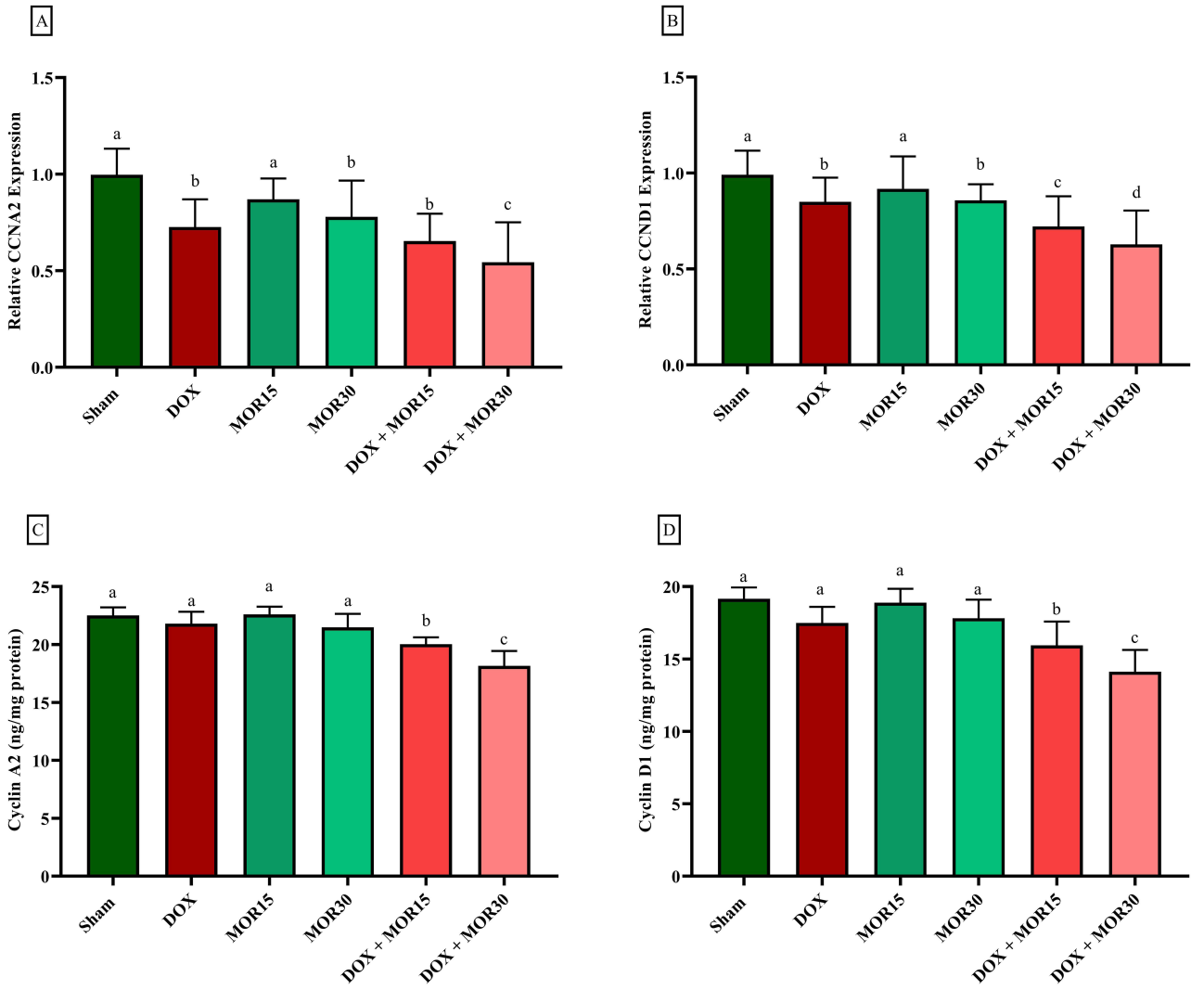

Figure 7 Cell cycle markers expression in tumor tissues. RT-qPCR analysis of (**A**) CCNA2 and (**B**) CCND1 gene expression. ELISA quantification of (**C**) Cyclin A2 and (**D**) Cyclin D1 protein levels in xenograft tumors. Data are expressed as mean ± SD (n=8). Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. Bars not sharing a common lowercase letter (a, b, c, d) are significantly different from each other ($p < 0.05$).

DOX and Morin Combination Promoted Autophagy in Ovarian Cancer Xenografts

The effects of DOX and morin on autophagy markers were evaluated in tumor tissues using qRT-PCR and ELISA (Figure 8). Gene expression analysis revealed that combination therapies significantly upregulated autophagy-related transcripts compared to monotherapy or Sham controls. DOX and MOR15 monotherapy induced modest, nonsignificant increases in *LC3* ($p > 0.05$) and *ATG5* ($p > 0.05$), while MOR30 monotherapy elevated *BECN1* expression by 1.41-fold ($p < 0.05$). Strikingly, the combination of DOX with MOR30 synergistically amplified *LC3* ($p < 0.001$), *ATG5* ($p < 0.001$), and *BECN1* ($p < 0.001$) mRNA levels compared to Sham. ELISA quantification of autophagy-related proteins corroborated these findings. Sham tumors exhibited baseline LC3 (12.3 ± 0.8 ng/mg), ATG5 (8.5 ± 0.6 ng/mg), and BECN1 (6.2 ± 0.5 ng/mg) protein levels. DOX and MOR15 monotherapy nonsignificantly increased ATG5 ($p > 0.05$) and BECN1 ($p > 0.05$), while MOR30 alone elevated all measured markers significantly ($p < 0.05$). In contrast, the DOX+MOR30 regimen profoundly upregulated LC3 ($p < 0.001$), ATG5 ($p < 0.001$), and BECN1 ($p < 0.001$) compared to all monotherapy groups. These results demonstrate that morin synergizes with DOX to potentiate autophagy activation in chemoresistant ovarian cancer xenografts, with the higher dose (30 mg/kg) eliciting the most robust effects ($p < 0.001$ vs DOX+MOR15).

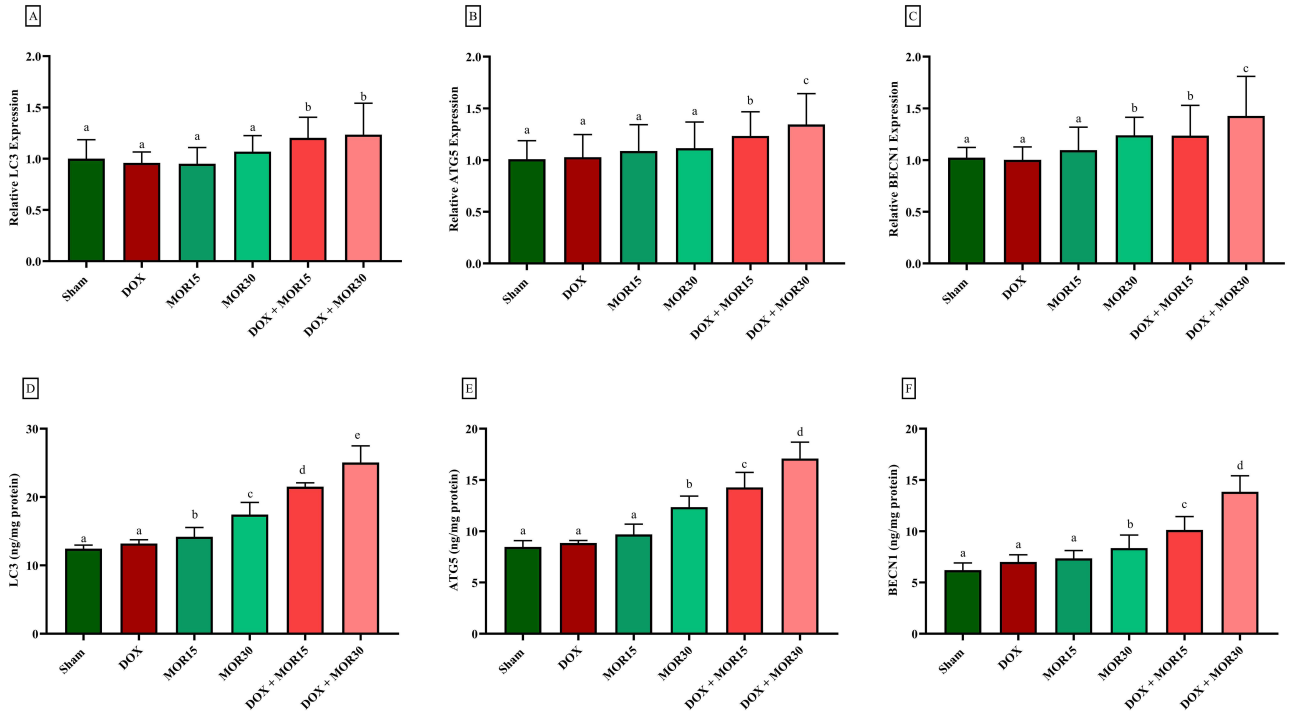

Figure 8 Combinational therapy promoted autophagy in xenograft models. qRT-PCR analysis of (**A**) LC3, (**B**) ATG5, and (**C**) BECN1 mRNA levels. ELISA quantification of (**D**) LC3, (**E**) ATG5, and (**F**) BECN1 protein levels in tumor tissues. Data are expressed as mean ± SD (n=8). Statistical significance was determined by one-way ANOVA with Tukey's post-hoc test. Bars not sharing a common lowercase letter (a, b, c, d) are significantly different from each other ($p < 0.05$).

Morin Counteracts DOX-Induced Oxidative Stress via Antioxidant Pathway Activation

The effects of DOX and morin on oxidative stress parameters were evaluated in tumor tissues (Table 2). Compared to the Sham group, DOX monotherapy reduced antioxidant enzyme activities, including SOD, CAT, GPx, and GR, while increasing lipid peroxidation ($p < 0.01$). Morin monotherapy (MOR15 and MOR30) dose-dependently restored antioxidant defenses. Combination therapies further amplified these effects. DOX+MOR30 synergistically enhanced SOD, CAT, GPx, and GR activities and elevated GSH levels compared to DOX alone ($p < 0.01$). GPx and GR levels in the DOX+MOR30 group surpassed those in both monotherapy groups ($p < 0.05$). Notably, DOX+MOR30 reduced MDA to 3.11 ± 0.63 nmol/mg protein, representing a 50.8% decrease relative to DOX monotherapy ($p < 0.001$). These findings demonstrate that morin, particularly at 30 mg/kg, counteracts DOX-induced oxidative stress by enhancing endogenous antioxidant systems and suppressing lipid peroxidation, with maximal efficacy observed in the combination regimen.

Table 2 Oxidative Stress Markers Across Treatment Groups

Group	SOD (U/mg)	CAT (U/mg)	GSH (nmol/mg)	GPx (U/mg)	GR (U/mg)	MDA (nmol/mg)
Sham	11.71 ± 0.67a	8.98 ± 0.61a	6.63 ± 0.72a	4.43 ± 0.71a	15.08 ± 0.59a	3.06 ± 0.37a
DOX	9.46 ± 0.79b	6.26 ± 1.12b	4.43 ± 1.13b	3.26 ± 0.64b	9.91 ± 0.87b	6.33 ± 0.85b
MOR15	12.06 ± 1.32a	9.09 ± 0.47a	7.45 ± 0.88a	4.93 ± 1.07a	17.48 ± 1.09a	3.24 ± 0.60a
MOR30	14.10 ± 1.73c	9.69 ± 1.24a	8.56 ± 1.50c	5.75 ± 0.92c	18.18 ± 1.31a	2.53 ± 0.54c
DOX+MOR15	11.30 ± 1.49a	7.94 ± 0.65a	5.73 ± 0.83a	4.00 ± 1.44a	12.90 ± 1.49a	4.69 ± 0.94d
DOX+MOR30	12.03 ± 1.55a	8.70 ± 1.07a	7.14 ± 0.79a	5.19 ± 1.58a,c	16.03 ± 2.02a	3.11 ± 0.63a

Notes: Data expressed as mean ± SD (n=8). For each parameter, means not sharing a common lowercase letter (a, b, c, d) are significantly different according to one-way ANOVA followed by Tukey's post-hoc test ($p < 0.05$).

https://doi.org/10.2147/CMAR.S567591

Discussion

EOC remains a formidable clinical challenge, accounting for over 90% of ovarian malignancies and ranking as the most lethal gynecological cancer due to late-stage diagnosis and chemoresistance recurrence.[27] While DOX retains utility in platinum-resistant settings, its clinical efficacy is hampered by dose-limiting cardiotoxicity, reproductive toxicity, and intrinsic resistance mechanisms.[28,29] These limitations underscore the urgent need for adjunctive therapies that enhance DOX's antitumor activity while mitigating adverse effects. Natural flavonoids, such as morin, have emerged as promising candidates due to their multi-targeted modulation of apoptosis, autophagy, and oxidative stress pathways.[22,30] The present study pioneers the oral co-administration of morin with DOX, demonstrating synergistic tumor suppression and reduced systemic toxicity in chemoresistant EOC models, a strategy that addresses both pharmacological and clinical gaps in current ovarian cancer management.

The synergistic cytotoxicity of morin and DOX observed in vitro aligns with emerging evidence that flavonoids enhance chemosensitivity in resistant ovarian cancer cells.[31,32] In vivo, the combination regimen significantly attenuated tumor progression, surpassing monotherapy effects, consistent with studies demonstrating flavonoid-mediated potentiation of conventional chemotherapeutics in xenograft models.[33,34] Notably, the preserved body weight and absence of overt toxicity in combinatorial groups contrast with the documented adverse effects of anthracyclines, underscoring morin's role in mitigating systemic compromise.[35,36] These findings collectively advocate for morin as a viable adjunct to optimize the therapeutic index of DOX in ovarian cancer. Furthermore, the combination therapy demonstrated an improved safety profile, as evidenced by the maintained body weight in mice receiving both DOX and morin, which contrasted with the significant weight loss observed in the DOX monotherapy group. This indicates that morin not only enhances the antitumor efficacy of DOX but also may mitigate its associated systemic toxicity, underscoring the potential for an improved therapeutic index.

The interplay of apoptosis and cell cycle dysregulation is central to chemotherapy resistance in ovarian cancer, with anti-apoptotic BCL-2 overexpression and defective caspase signaling frequently undermining therapeutic efficacy.[37,38] In this study, morin's ability to suppress BCL-2, a key mediator of chemoresistance, while concurrently activating CASP-3 and CASP-9 aligns with emerging strategies to re-sensitize refractory tumors. Recent studies highlight that BCL-2 inhibition is critical for reversing resistance, as its overexpression shields cancer cells from intrinsic apoptosis, even in the presence of DNA-damaging agents like doxorubicin.[39,40] Notably, the observed CASP activation suggests restoration of mitochondrial apoptosis, a mechanism often disrupted in resistant phenotypes, as corroborated by preclinical models using quercetin to enhance caspase-dependent cell death.[41] These findings position morin as a dual-action adjuvant, simultaneously dismantling anti-apoptotic defenses and reactivating latent apoptotic machinery, a strategy distinct from single-target inhibitors currently under investigation. Equally significant is morin's capacity to induce cell cycle arrest via Cyclin A2 and D1 suppression, which disrupts proliferative signaling in chemoresistant cells. Cyclin D1, a driver of G1/S transition, is frequently overexpressed in platinum-resistant ovarian cancer, promoting unchecked proliferation and therapy evasion.[42] The combinatorial regimen's suppression of these cyclins mirrors findings with resveratrol, quercetin, and fisetin, other flavonoids shown to arrest cell cycle progression in refractory models.[43] However, the present study advances this paradigm by demonstrating that morin not only halts proliferation but also synergizes with doxorubicin to amplify stress-induced autophagy, thereby creating a multi-pronged assault on tumor survival. This dual modulation of apoptosis and cell cycle pathways addresses a critical gap in adjuvant therapy, where monotherapy often fails to counteract the redundancy of resistance mechanisms. The translational implications are profound: by targeting BCL-2, CASPs, and cyclins within a single regimen, morin reduces the effective dose of doxorubicin required for tumor control, potentially mitigating dose-dependent toxicities. This approach contrasts with recent efforts focusing on synthetic BCL-2 inhibitors (eg, venetoclax), which, while effective, lack the pleiotropic benefits of flavonoids and carry risks of on-target hematological toxicity.[44,45] Furthermore, the in vivo preservation of systemic health metrics, such as stable body weight, underscores morin's protective role against chemotherapy-induced stress, a feature seldom reported in studies of synthetic adjuvants. Collectively, these data position morin not merely as a chemosensitizer but as a holistic modulator of tumor biology, offering a clinically feasible strategy to enhance therapeutic outcomes in a patient population with limited options.

The interplay between autophagy, oxidative stress, and apoptosis is pivotal in chemoresistant ovarian cancer, where dysregulated survival pathways often render monotherapies ineffective. In this study, the combination of morin and DOX caused a robust upregulation of autophagic markers (LC3, ATG5, BECN1), indicating the induction of autophagy initiation. The functional association of this induction with enhanced apoptosis and tumor suppression suggests a shift toward pro-death autophagy. However, as autophagic flux was not directly measured, the possibility of altered lysosomal degradation contributing to this profile cannot be entirely excluded. Autophagy typically exhibits a dual role in cancer: early-stage tumors exploit it for stress mitigation, while advanced malignancies rely on its cytoprotective functions to evade therapy.[37] However, sustained autophagic flux, as observed here, can transition to lethal autophagy, wherein excessive self-digestion overwhelms cellular repair mechanisms, synergizing with apoptosis to induce cell death.[37] This aligns with recent findings where flavonoid-induced autophagy (eg, quercetin, apigenin) cooperated with caspase activation to overcome resistance in ovarian and breast cancers, particularly in models with defective apoptosis signaling.[46–48] The combinatorial regimen's ability to suppress oxidative stress, evidenced by restored SOD, CAT, and GSH activity alongside reduced MDA, further underscores its mechanistic novelty. This significant mitigation of oxidative damage is not only crucial for overcoming chemoresistance in tumor cells but also holds important clinical implications for reducing doxorubicin's systemic toxicity. Doxorubicin-induced cardiotoxicity is primarily driven by oxidative stress and lipid peroxidation in cardiac tissue.[28] The ability of morin to potently enhance endogenous antioxidant defenses and reduce MDA, as demonstrated in our study, is consistent with mechanisms shown to confer cardioprotection in preclinical models.[49] The preserved body weight in our combination treatment groups further supports improved systemic tolerability. Thus, morin may offer a dual benefit: sensitizing resistant tumors while concurrently protecting against doxorubicin's dose-limiting cardiotoxic effects. DOX generates cytotoxic ROS, which, while damaging DNA, also activate Nrf2/KEAP1-mediated antioxidant responses in cancer cells, paradoxically fostering survival.[50,51] Morin's antioxidant properties likely disrupt this feedback loop by directly scavenging ROS and enhancing endogenous defenses, thereby preventing Nrf2-driven adaptation. This dual modulation creates a "stress overload"; DOX-induced DNA damage is amplified, while morin blocks compensatory survival signals, forcing cells toward apoptotic or autophagic death. Such a strategy mirrors recent approaches using luteolin to sensitize cancer cells to gemcitabine by concurrently targeting ROS and autophagy.[52,53] The synergy between autophagy and apoptosis in this context may involve crosstalk at the BCL-2 nexus. BCL-2, an anti-apoptotic protein, also inhibits autophagy by binding BECN1.[54,55] Morin's suppression of BCL-2, as demonstrated here, liberates BECN1 to initiate autophagy while freeing pro-apoptotic BAX/BAK to activate caspases. This dual "release" mechanism, observed in studies with fisetin and venetoclax, explains the combinatorial regimen's superior efficacy compared to monotherapy.[56,57] Furthermore, autophagy may degrade key anti-apoptotic proteins (eg, MCL-1) or damaged organelles, priming cells for CASP-3/9 activation.[58,59] Such cross-activation is critical in chemoresistant EOC, where mitochondrial apoptosis is often impaired. Potential upstream signaling nodes include the AMPK/mTOR and PI3K/AKT pathways, which regulate both autophagy and oxidative stress. Morin's flavonoid structure suggests AMPK activation, inhibiting mTOR to induce autophagy, while simultaneously suppressing PI3K/AKT to block pro-survival signaling—a hypothesis supported by studies on analogous compounds.[60] Additionally, flavonoids may modulate the p62/KEAP1/Nrf2 axis, where p62 accumulation (via autophagy inhibition) stabilizes Nrf2 to enhance antioxidant responses. By promoting autophagic clearance of p62, morin could destabilize Nrf2, sensitizing cells to oxidative damage—a mechanism recently implicated in resveratrol's chemosensitizing effects.[61]

While this study provides mechanistic insights, several questions remain. First, the precise signaling pathways linking morin's antioxidant effects to autophagy induction (eg, AMPK/mTOR vs HIF-1α/BNIP3) require validation using phosphoproteomics or pathway-specific inhibitors. Second, while our in vitro work included both sensitive (A2780, OVCAR-3) and resistant (OVCAR-3-DR) lines, the generalizability of our findings would be strengthened by future studies incorporating additional chemoresistant cell lines (eg, A2780-ADR) or patient-derived organoids to better reflect the heterogeneity of EOC. Moreover, future studies would benefit from including non-tumorigenic cell lines (eg, IOSE80) to more formally quantify the therapeutic window and confirm the selective safety of the morin-doxorubicin combination. Third, the temporal relationship between autophagy and apoptosis, whether they occur sequentially or concomitantly, was not delineated. Live-cell imaging or time-course assays could clarify this interplay. Also, present interpretation of autophagy is based on marker expression, thereby future studies employing flux assays (eg, LC3

turnover or p62 degradation) are warranted to precisely define the dynamics and completion of the autophagic process in this context. Additionally, future investigations would benefit from histopathological analyses (eg, H&E, TUNEL) of tumor sections to provide direct visual correlation with the molecular and biochemical markers of apoptosis and treatment response. Furthermore, while this study demonstrates synergistic modulation of apoptosis, autophagy, and the cell cycle, the precise upstream signaling pathways (eg, AMPK/mTOR, PI3K/AKT) through which morin exerts these pleiotropic effects remain to be fully elucidated and represent a key direction for future mechanistic research. Finally, while existing literature confirms the oral bioavailability of morin, dedicated pharmacokinetic and pharmacodynamic (PK/PD) studies of the morin-doxorubicin combination are needed to define optimal dosing schedules and fully assess the clinical translatability of this synergistic regimen.

Conclusion

The integration of morin with doxorubicin elicited potent antitumor effects in chemoresistant ovarian cancer models, synergistically enhancing apoptosis (BCL-2 suppression, caspase-3/9 activation), inducing pro-death autophagy (LC3, ATG5, BECN1 upregulation), and arresting cell cycle progression (Cyclin A2/D1 downregulation), while concurrently mitigating doxorubicin-induced oxidative stress via restoration of SOD, CAT, GPx, GR, and GSH activity and suppression of lipid peroxidation (MDA). This dual targeting of survival and stress pathways not only overcame intrinsic chemoresistance but also preserved systemic health, as evidenced by stable body weight, contrasting the toxicity of doxorubicin monotherapy. These findings position morin as a promising, orally bioavailable adjunct worthy of further investigation, including combinatorial PK/PD studies, to advance its translation for the treatment of refractory EOC.

Data Sharing Statement

The datasets utilized and/or examined during this study can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The current study was designed and conducted in accordance with international guidelines pertaining to animal welfare and the National Institute of Health (NIH). The use of animals and the procedures involved in this study were evaluated and sanctioned by the local ethics committee (Zhinanzhen Biology Ethics Committee, No: A2025000056), and were carried out in compliance with ARRIVE guidelines.

Author Contributions

All authors made a significant contribution to the present study, 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

There is no funding to report.

Disclosure

The authors affirm that they have no competing interest in this work.

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