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Berberine Curtails Ovarian Tumor Rebound by Rewiring COX-2-Linked Macrophage Responses

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Abstract

Background: Paclitaxel (PTX), widely used in ovarian cancer treatment, may unintentionally promote tumor recurrence by creating conditions that support the growth of surviving malignant cells. This study investigated interactions among apoptotic tumor cells, residual cancer cells, and macrophages while examining the therapeutic effects of berberine.

Methods: A Truswell co-culture model incorporating PTX-exposed SKOV3 cells, surviving SKOV3 cells, and THP-1-derived macrophages was developed. Additionally, a mouse xenograft model containing apoptotic and ID8 tumor cells was employed to assess berberine activity.

Results: PTX-induced apoptosis enhanced residual tumor cell proliferation through the caspase-3/iPLA2/AA/COX-2/PGE2 signaling cascade and encouraged macrophage differentiation toward the tumor-supportive M2 phenotype. Berberine effectively interrupted these responses, reducing cancer cell repopulation and PGE2-dependent M2 polarization across experimental models.

Conclusion: These findings identify berberine as a promising adjunct to conventional chemotherapy, potentially limiting treatment-associated tumor regrowth and immunosuppressive macrophage responses. Its established pharmacological profile supports further investigation into its suitability for prolonged maintenance strategies in ovarian cancer management, although additional clinical validation remains essential before therapeutic implementation.

Keywords: Berberine; Ovarian Cancer; Tumor Repopulation; M2 Macrophage Polarization; Prostaglandin E2.

INTRODUCTION

Ovarian cancer continues to be among the most life-threatening gynecological cancers worldwide, largely because it is frequently diagnosed at an advanced stage and is associated with substantial mortality [1]. Paclitaxel (PTX)-based chemotherapy remains an important component of treatment for advanced ovarian malignancies. Although many patients initially experience considerable tumor reduction following chemotherapy, disease recurrence and metastatic progression frequently compromise long-term therapeutic success. Emerging evidence indicates that chemotherapy can produce opposing biological effects. While cytotoxic agents eliminate malignant cells through apoptosis, they may also establish conditions that encourage the regeneration of surviving tumor populations [2-4]. This phenomenon, commonly described as chemotherapy-associated tumor repopulation, involves the release of growth-promoting molecular signals from

dying cancer cells, which stimulate the expansion of residual malignant cells [4]. Understanding how apoptotic cells influence neighboring tumor populations is therefore essential for identifying therapeutic approaches that may reduce recurrence following ovarian cancer treatment.

The biological consequences of chemotherapy-induced apoptosis extend beyond the elimination of damaged cells. Activated caspase-3, traditionally recognized for its central involvement in programmed cell death, can also participate in molecular signaling events that promote the proliferation of surviving cancer cells within the tumor microenvironment (TME) [5]. One proposed mechanism involves caspase-3-dependent activation of calcium-independent phospholipase A2 (iPLA2), which facilitates arachidonic acid (AA) metabolism and increases the production of prostaglandin E2 (PGE2) [6]. Elevated PGE2 concentrations can subsequently activate proliferative signaling networks in neighboring malignant cells, contributing to tumor regeneration despite continued cytotoxic pressure [7,8]. These observations suggest that the apoptotic response to chemotherapy may unintentionally create a biochemical environment favorable to cancer cell survival and expansion.

Alongside its effects on malignant cell proliferation, chemotherapy can substantially modify the immune composition and functional characteristics of the TME [9]. Tumor-associated macrophages (TAMs) represent a particularly important immune population because of their capacity to adopt different functional states in response to surrounding molecular signals [10]. Macrophages exhibiting M2-like characteristics are frequently associated with immunosuppression, tissue remodeling, angiogenesis, and tumor progression. Their accumulation within malignant tissues may contribute to the establishment of conditions that support cancer cell repopulation and therapeutic resistance [11,12]. Nevertheless, the mechanisms through which chemotherapy-damaged or apoptotic tumor cells influence macrophage behavior remain incompletely characterized. In particular, the contribution of soluble mediators released by dying cancer cells to macrophage recruitment, phenotypic changes, and tumor-promoting activity requires further investigation. Clarifying these interactions could reveal important connections between apoptosis-associated signaling and the development of an immunosuppressive tumor environment.

Addressing chemotherapy-associated recurrence may therefore require therapeutic interventions that target both residual malignant cells and the supportive immune populations within the TME [13]. Berberine, a naturally occurring isoquinoline alkaloid, has attracted increasing research interest because of its reported antiproliferative, anti-inflammatory, and immunomodulatory properties [14]. Experimental investigations suggest that berberine can influence several molecular pathways involved in cancer progression, making it a potential candidate for combination treatment strategies. Its history of pharmacological use has also encouraged interest in its possible application during prolonged therapeutic management. However, the transition from initial chemotherapy response to recurrent malignancy often develops over an extended period, creating difficulties for sustained administration of conventional cytotoxic treatments because of cumulative adverse effects. Although berberine may offer advantages in this context, its long-term safety, optimal dosage, bioavailability, and clinical effectiveness in ovarian cancer require careful evaluation [15].

The potential relationship between berberine activity, apoptosis-driven cancer cell repopulation, and macrophage polarization presents an important area for investigation. Chemotherapy-induced tumor cell death may initiate a sequence of interconnected molecular events in which caspase-3 activation enhances AA metabolism, promotes COX-2-associated PGE2 production, and stimulates the proliferation of residual malignant cells. Simultaneously, factors released into the surrounding microenvironment may influence macrophage polarization toward an M2-like phenotype, further supporting tumor progression. Determining whether these events arise through shared or interacting molecular pathways could improve understanding of the complex biological responses that follow PTX exposure.

The present study investigated whether PTX-induced apoptosis in SKOV3 ovarian cancer cells promotes residual tumor cell proliferation and alters macrophage polarization through signaling associated with the caspase-3/iPLA2/AA/COX-2/PGE2 pathway. An in vitro Transwell co-culture system was established to examine interactions among apoptotic ovarian cancer cells, surviving malignant cells, and THP-1-derived macrophages. In addition, an in vivo xenograft model incorporating apoptotic and ID8 ovarian cancer cells was used to evaluate the effects of berberine on tumor growth and the associated microenvironment. Attention was directed toward determining whether berberine could interfere with apoptosis-induced proliferative signaling while simultaneously limiting PGE2-associated M2 macrophage polarization. By examining these interconnected processes, the study sought to

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clarify molecular mechanisms that may contribute to chemotherapy-associated ovarian tumor recurrence and assess the experimental potential of berberine as an adjunct to conventional anticancer treatment.

MATERIALS AND METHODS

Chemicals and Reagents

Berberine (Cat. No. IB0120) was purchased from Solarbio Science & Technology Co., Ltd. (Beijing, China). For cell-based experiments, a 200 μM stock solution was prepared in culture medium containing 0.2% dimethyl sulfoxide (DMSO). Paclitaxel (PTX; Cat. No. 580555) was obtained from Sigma (St. Louis, MO, USA). Enzyme-linked immunosorbent assay (ELISA) kits for human prostaglandin E2 (PGE2; Cat. No. NBP3-00375), mouse PGE2 (Cat. No. NBP3-00428), and arachidonic acid (AA; Cat. No. NBP2-59872) were obtained from the indicated commercial suppliers.

The primary antibody against calcium-independent phospholipase A2 (iPLA2; Cat. No. 22030-1-AP) was supplied by Proteintech (Rosemont, IL, USA). Antibodies targeting caspase-3 (Cat. No. ab184718), GLI1 (Cat. No. ab289368), cyclooxygenase-2 (COX-2; Cat. No. ab179800), arginase-1 (Arg-1; Cat. No. ab212522), transforming growth factor-beta (TGF-β; Cat. No. ab315254), CD163 (Cat. No. ab182422), Ki67 (Cat. No. ab16667), CD206 (Cat. No. ab64693), F4/80 (Cat. No. ab300412), and β-actin (Cat. No. ab8227) were obtained from Abcam (Cambridge, UK). Primary antibodies were diluted at 1:1000 before application.

Rabbit IgG isotype control recombinant antibody (Cat. No. 98136-RR), CoraLite488-conjugated goat anti-rabbit IgG (H+L; Cat. No. SA00013-2), and rhodamine (TRITC)-conjugated goat anti-rat IgG (H+L; Cat. No. SA00007-7) were purchased from Proteintech (Rosemont, IL, USA). Dulbecco's Modified Eagle Medium (DMEM; Cat. No. 1196092), RPMI-1640 medium (Cat. No. 12633012), and fetal bovine serum (FBS; Cat. No. A5256701) were supplied by Gibco (Thermo Fisher Scientific, Waltham, MA, USA). All chemicals and reagents used in the experiments were of analytical grade.

Cell Culture and Maintenance

Human ovarian cancer SKOV3 cells were maintained in DMEM supplemented with 10% FBS and 1% penicillin–streptomycin solution, providing final concentrations of 100 U/mL penicillin and 100 μg/mL streptomycin. The human monocytic cell line THP-1 was cultured in RPMI-1640 medium containing 10% FBS, 1% penicillin–streptomycin, and 0.05 mM β-mercaptoethanol; Thermo Fisher Scientific, Waltham, MA, USA).

Murine ovarian cancer ID8 cells were propagated in DMEM supplemented with 4% FBS, 1% insulin–transferrin–selenium (Cat. No. 41400045; Thermo Fisher Scientific, Waltham, MA, USA), and 1% penicillin–streptomycin. All cell cultures were maintained in a humidified incubator at 37°C under an atmosphere containing 5% CO_2 and 95% air.

To maintain experimental reliability, cell line identities were verified through short tandem repeat (STR) profiling before experimentation. Routine testing for mycoplasma contamination was performed using a commercially available detection kit (Vazyme, Nanjing, China). All cell cultures remained free of detectable mycoplasma contamination throughout the experimental period.

Transwell Co-Culture Model

A Transwell co-culture system (Corning, NY, USA) equipped with semipermeable membrane inserts containing 0.4 μm pores was employed to investigate interactions between chemotherapy-exposed ovarian cancer cells and recipient cell populations. The experimental configuration permitted the movement of soluble signaling molecules between chambers while preventing direct cellular contact.

SKOV3 cells exposed to PTX were positioned in the lower compartment and served as feeder cells. Untreated SKOV3 cells or THP-1-derived macrophages were cultured separately in the upper inserts as recipient cells. This arrangement was designed to assess the influence of apoptosis-associated soluble factors on residual cancer cell proliferation and macrophage polarization [16].

Preparation of Apoptotic Feeder Cells

SKOV3 cells were introduced into the lower compartments of six-well culture plates at a density of 2×10^5 cells per well in 2.0 mL of complete growth medium. To generate an apoptotic feeder cell population, the cultures were exposed to 20 nmol/L PTX for 24 hours.

Following chemotherapy exposure, the cells were washed three times with phosphate-buffered saline (PBS) to eliminate residual PTX. The treated SKOV3 cells were subsequently used as feeder cells in the Transwell system to examine the paracrine effects of chemotherapy-induced apoptosis on neighboring cell populations.

Co-Culture Conditions and Berberine Treatment

Untreated SKOV3 cells or THP-1-derived macrophages

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were seeded into the upper Transwell inserts at a concentration of 1×10^4 cells per well in 1.5 mL of complete culture medium. After overnight incubation, the inserts were transferred into the corresponding lower chambers containing PTX-treated feeder cells.

For groups receiving pharmacological intervention, berberine was introduced into both the upper and lower chambers at a final concentration of 5 μmol/L when co-culture was initiated. This approach ensured exposure of both cellular compartments to the compound.

The co-culture system was maintained for 48 hours under standard incubation conditions. At the end of the treatment period, feeder cells, recipient cells, and culture supernatants were collected for subsequent molecular and biochemical examinations. Recipient cells attached to the Transwell membranes were fixed with methanol and processed for immunofluorescence staining of Ki67 or CD206 to evaluate cellular proliferation and macrophage phenotypic characteristics, respectively [17-21].

In-Vivo Evaluation of Antitumor Activity

Animal experiments were conducted following approval from the Institutional Animal Care and Use Committee of Dalian University of Technology (Approval No. DUTFM260525-03). All procedures were performed in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals.

To investigate apoptosis-associated tumor repopulation in vivo, 1×10^5 ID8 ovarian cancer cells were exposed to 20 nmol/L PTX for 24 hours. Following treatment, all cellular material, including apoptotic cells present in the suspension and supernatant, was collected and combined with 2×10^6 untreated ID8 cells. The resulting cell preparation was resuspended in 70 μL PBS (pH 7.2) and combined with Matrigel Matrix, reported at a concentration of 70 μmol/L. This preparation constituted the apoptosis-associated experimental group (Apo). A separate preparation containing 2×10^6 untreated ID8 cells served as the control group (Con).

The prepared cell suspensions were administered by subcutaneous injection into one dorsal flank of eight-week-old female C57BL/6 mice. When established tumors reached approximately 60–100 mm^3, animals assigned to the treatment group received berberine at a dosage of 100 mg/kg by daily oral gavage. Animals in the corresponding control group received an equivalent administration of saline.

Mouse body weights and tumor dimensions were assessed at three-day intervals. Tumor volumes were estimated using the following equation:

$$\text{Tumor Volume } (mm^3) = \text{Length} \times \text{Width}^2 \times 0.52$$

Animals were euthanized 25 days after treatment initiation. Immediately before euthanasia, blood specimens were collected through the orbital sampling procedure described in the experimental protocol. The blood samples were maintained at room temperature for 30 minutes to permit clot formation, followed by centrifugation at 3000 rpm for 15 minutes at 4°C.

Separated serum samples were transferred to storage at −80°C until biochemical measurements were performed. Tumor tissues were also excised and preserved at −80°C for subsequent experimental analyses [22-30].

Immunofluorescence Staining

Immunofluorescence analysis was conducted to examine the expression and cellular distribution of selected proteins in tumor tissue specimens. Paraffin-embedded tumor sections were initially deparaffinized, rehydrated, and subjected to antigen retrieval.

To minimize nonspecific antibody interactions, tissue sections were incubated with 10% bovine serum albumin (BSA) for one hour. Subsequently, the sections were exposed to the appropriate primary antibodies and maintained at 4°C overnight.

After three washes with PBS containing Tween (PBST), the sections were incubated with fluorescence-labeled secondary antibodies for one hour. Following additional washing, nuclear counterstaining was performed using 4′,6-diamidino-2-phenylindole (DAPI; 1 μg/mL) for five minutes.

Fluorescence images were obtained using an EVOS M5000 imaging system (Invitrogen, Thermo Fisher Scientific). Quantitative assessment of fluorescence intensity was carried out using ImageJ software.

Immunohistochemical Analysis

Immunohistochemical staining was performed to characterize protein expression in tumor tissues. Excised specimens were fixed in 4% paraformaldehyde for 24 hours, processed through routine paraffin embedding, and sectioned at a thickness of 4 μm.

The prepared sections were treated with xylene to remove paraffin and subsequently rehydrated through decreasing concentrations of ethanol. Antigen recovery was performed by heating the sections in 10 mM sodium citrate buffer (pH

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6.0) using a microwave oven for 15 minutes.

After the slides had cooled to room temperature, endogenous peroxidase activity was inhibited by incubation with 3% hydrogen peroxide (H_2O_2) for 10 minutes. Nonspecific binding was minimized through treatment with 5% BSA for one hour at room temperature.

Tissue sections were then incubated overnight at 4°C with the corresponding primary antibodies. After three PBS washes, horseradish peroxidase (HRP)-conjugated secondary antibodies were applied for one hour at room temperature.

Immunoreactive proteins were visualized using a 3,3′-diaminobenzidine (DAB) detection kit (Cat. No. DA1010; Solarbio, Beijing, China). Hematoxylin was used for nuclear counterstaining. The sections were subsequently dehydrated, cleared with xylene, and mounted for microscopic examination [13].

Stained specimens were examined using an EVOS M5000 microscope (Invitrogen, Thermo Fisher Scientific), and representative images were recorded. For quantitative evaluation, at least three randomly selected high-power microscopic fields were examined from each section. ImageJ software was used to determine the extent of positive immunohistochemical staining.

Western Blot Analysis

Western blotting was performed to measure the expression of proteins involved in apoptosis-associated signaling and macrophage polarization. Total cellular proteins were isolated from the experimental groups using radioimmunoprecipitation assay (RIPA) lysis buffer containing protease and phosphatase inhibitors (Cat. No. R0020; Solarbio, Beijing, China).

Protein concentrations were measured using a bicinchoninic acid (BCA) assay kit (Cat. No. PC0020; Solarbio, Beijing, China) following the manufacturer's protocol. The extracted proteins were combined with loading buffer and subjected to heat-induced denaturation before electrophoretic separation.

Protein samples were separated using sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) with gel concentrations ranging from 7.5% to 12.5%. Following electrophoresis, the separated proteins were transferred onto polyvinylidene fluoride (PVDF) membranes.

The membranes were blocked with BSA for two hours to reduce nonspecific antibody binding. They were subsequently incubated with the appropriate primary antibodies overnight at 4°C. After washing, the membranes were exposed to corresponding secondary antibodies for one hour at room temperature.

Protein bands were detected using an enhanced chemiluminescence (ECL) detection system and visualized with a Tanon 4600 imaging instrument (Shanghai, China). Densitometric measurements of the detected bands were performed for quantitative analysis of protein expression [14].

Enzyme-Linked Immunosorbent Assay

ELISA was employed to determine the concentrations of PGE2 and AA in collected cell culture supernatants and serum samples. The samples were processed using the respective commercially available assay kits according to the manufacturers' instructions.

Following completion of the assay reactions, absorbance values were measured at 450 nm using a Multiskan SkyHigh microplate reader (Thermo Fisher Scientific, Waltham, MA, USA). The resulting measurements were used to evaluate changes in PGE2 production and AA levels associated with chemotherapy exposure and berberine administration [15,16].

Plasmid Transfection and Cox-2 Overexpression

To examine the functional contribution of COX-2 signaling, a COX-2 overexpression plasmid and its corresponding empty vector control were obtained from GenePharma (Shanghai, China).

SKOV3 cells were plated in six-well culture dishes and allowed to proliferate until approximately 60%–70% confluence was achieved. Plasmid transfection was conducted using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) in accordance with the supplier's recommendations.

For each well, 2 μg of plasmid DNA and the appropriate quantity of transfection reagent were separately diluted in Opti-MEM reduced-serum medium (Gibco, Grand Island, NY, USA). The diluted preparations were gently combined and maintained at room temperature for 15 minutes to facilitate the formation of DNA–lipid complexes.

The resulting transfection mixture was added dropwise to the cultured cells. After six hours of incubation, the transfection medium was removed and replaced with complete growth medium. The transfected SKOV3 cells were subsequently prepared for use as feeder cells in the Transwell co-culture experiments.

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STATISTICAL ANALYSIS

Statistical evaluation was carried out using GraphPad Prism software, version 8.0. Experimental findings were expressed as mean ± standard deviation (SD) based on three independent experiments. A probability value of $P < 0.05$ was considered indicative of statistical significance.

RESULTS

Paclitaxel-Induced Apoptosis Enhances the Repopulation of Skov3 Ovarian Cancer Cells

Previous investigations have indicated that apoptotic malignant cells can stimulate tumor regeneration by promoting the proliferation of residual cancer cells that survive cytotoxic treatment [3]. To investigate this phenomenon, a Transwell co-culture model was established using paclitaxel (PTX)-treated SKOV3 cells as apoptotic feeder cells and untreated SKOV3 cells as recipient cells. Immunofluorescence analysis revealed a marked increase in Ki67 expression in recipient cells exposed to PTX-treated feeder cells compared with the untreated control group, indicating enhanced proliferative activity (Figure 1).

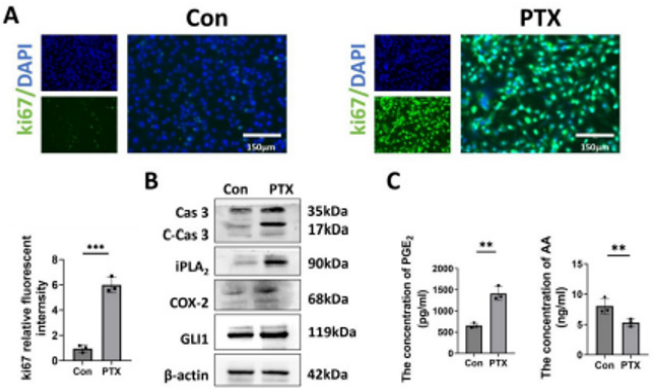


Figure 1: PTX accelerated the population of ovarian cell lines. (A) Ki67 expression in receptor cells. (B) protein expression of feeder cells (caspase 3, iPLA2 and COX-2) and receptor cells (GLI1). (C) The AA and PGE2 levels in supernatants.

To examine the molecular events associated with this response, the expression of apoptosis-related proteins and mediators involved in arachidonic acid metabolism was evaluated. Western blot analysis demonstrated increased activation of caspase-3 in PTX-exposed feeder cells, confirming the involvement of apoptotic signaling following chemotherapy treatment (Figure 1). Further examination revealed elevated expression of calcium-independent phospholipase A2 (iPLA2) and cyclooxygenase-2 (COX-2) in the PTX-treated feeder cell population relative to the control group (Figure 1A) [19].

Biochemical analysis of the culture supernatants identified changes in arachidonic acid (AA) metabolism following PTX exposure. Specifically, AA concentrations were reduced, whereas prostaglandin E2 (PGE2) levels increased in the experimental group (Figure 1B). These findings suggest enhanced conversion of AA into downstream prostaglandin products under chemotherapy-associated apoptotic conditions.

The expression of GLI1, a transcriptional regulator associated with proliferative signaling and potentially influenced by PGE2-mediated pathways, was also examined in recipient SKOV3 cells. Increased GLI1 protein expression was detected following exposure to apoptotic feeder cells, suggesting activation of proliferation-associated molecular responses (Figure 1C). These observations indicate that PTX-induced apoptosis creates a signaling environment favorable to the expansion of surviving ovarian cancer cells. The coordinated changes in caspase-3 activation, iPLA2 and COX-2 expression, AA availability, and PGE2 production support the involvement of the caspase-3/iPLA2/AA/COX-2/PGE2 signaling axis in chemotherapy-associated tumor cell repopulation.

Apoptotic Skov3 Cells Facilitate M2-Like Macrophage Polarization

Macrophages exhibiting M2-like characteristics contribute to the establishment of tumor-supportive microenvironments and may facilitate malignant progression following chemotherapy. However, the ability of chemotherapy-induced apoptotic ovarian cancer cells

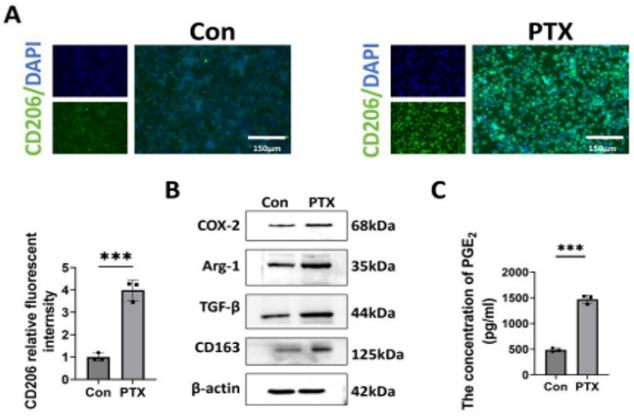


Figure 2: Berberine inhibits PTX-induced reproliferating of ovarian cell lines. (A) Ki67 expression of receptor cells. (B) protein expression of cells (feeder cells for COX-2 and receptor cells for GLI1). (C) The AA and PGE2 levels in supernatants. * P<0.001.

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to influence macrophage polarization requires further clarification. To investigate this relationship, THP-1-derived macrophages were cultured in the upper compartment of a Transwell system, while PTX-treated SKOV3 cells were maintained as feeder cells in the lower chamber.

Immunofluorescence staining demonstrated that macrophages exposed to apoptotic SKOV3 cells exhibited significantly increased expression of CD206, a commonly used marker associated with M2-like macrophage polarization. The intensity of CD206 staining was considerably greater in the model group than in the control group, indicating a shift toward an alternatively activated macrophage phenotype (Figure 2A).

Additional protein expression analysis revealed increased levels of arginase-1 (Arg-1), transforming growth factor-beta (TGF-β), and CD163 in macrophages maintained in the apoptotic tumor cell co-culture environment (Figure 2B). These molecular changes were consistent with the acquisition of M2-associated characteristics and suggested that soluble factors released from chemotherapy-damaged ovarian cancer cells could influence macrophage functional responses (Figure 2A).

To explore the potential contribution of prostaglandin signaling, COX-2 expression was assessed in PTX-treated SKOV3 feeder cells. Increased COX-2 protein expression was observed following chemotherapy exposure, indicating activation of a major enzyme involved in prostaglandin synthesis (Figure 2B). Consistent with this finding, ELISA measurements demonstrated elevated PGE2 concentrations in culture supernatants obtained from the model group compared with the untreated control group (Figure 2C).

These findings suggest that apoptosis-associated molecular signals released by PTX-treated ovarian cancer cells contribute to the development of an M2-like macrophage phenotype. The simultaneous elevation of COX-2 expression and extracellular PGE2 levels supports a potential role for prostaglandin-mediated signaling in connecting chemotherapy-induced tumor cell apoptosis with macrophage polarization [20].

Berberine Suppresses Paclitaxel-Associated Repopulation of Surviving Ovarian Cancer Cells

After establishing that PTX-induced apoptotic cells enhanced the proliferation of surviving SKOV3 cells, the potential inhibitory effects of berberine were examined using the same Transwell co-culture model. Berberine was administered at a concentration of 5 μmol/L to both chambers of the experimental system to evaluate its influence on apoptosis-associated tumor cell repopulation.

Ki67 immunofluorescence staining demonstrated substantially greater proliferative activity in recipient SKOV3 cells exposed to PTX-treated feeder cells compared with the untreated control group (Figure 3A). However, berberine supplementation markedly reduced Ki67 expression in recipient cells within the PTX-treated co-culture system, indicating suppression of the proliferative response induced by apoptotic tumor cells. In contrast, exposure to berberine alone at the same concentration did not produce an appreciable change in recipient SKOV3 cell proliferation relative to untreated controls (Figure 3).

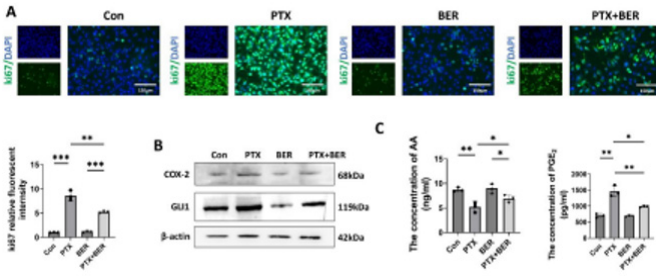


Figure 3: Berberine inhibits PTX-induced reproliferating of ovarian cell lines. (A) Ki67 expression of receptor cells. (B) protein expression of cells (feeder cells for COX-2 and receptor cells for GLI1). (C) The AA and PGE2 levels in supernatants. * P<0.001.

To investigate the molecular basis of this inhibitory activity, proteins associated with prostaglandin-dependent proliferative signaling were analyzed. Recipient SKOV3 cells in the PTX model group exhibited increased COX-2 and GLI1 protein expression (Figure 3A). The addition of berberine partially reduced these elevations, suggesting attenuation of signaling events associated with chemotherapy-induced tumor cell repopulation (Figure 3B).

The influence of berberine on AA metabolism and PGE2 production was further assessed through biochemical analysis of culture supernatants. Treatment with berberine alone did not significantly alter AA or PGE2 concentrations compared with the untreated control group (Figure 3C). In contrast, exposure to PTX-induced apoptotic feeder cells was associated with lower AA concentrations and increased PGE2 production. These chemotherapy-associated changes were partially reversed following berberine administration, with AA levels recovering and PGE2 concentrations declining relative to the PTX model group (Figure 3C).

The observed reduction in Ki67 expression, together with

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the attenuation of COX-2 and GLI1 protein expression and alterations in prostaglandin metabolism, indicates that berberine interferes with molecular processes involved in apoptosis-driven cancer cell repopulation. These findings support the potential involvement of the AA/COX-2/PGE2/GLI1 signaling pathway in the antiproliferative effects of berberine within the chemotherapy-associated ovarian cancer microenvironment.

Berberine Attenuates Paclitaxel-Induced M2-Like Macrophage Polarization

The preceding experiments demonstrated that apoptotic SKOV3 cells promote the expression of macrophage markers associated with M2-like polarization. Based on these observations, subsequent experiments examined whether berberine could counteract the macrophage phenotypic changes induced by PTX-treated ovarian cancer cells.

Immunofluorescence analysis revealed increased CD206 expression in THP-1-derived macrophages exposed to apoptotic SKOV3 feeder cells. This response was substantially reduced following treatment with 5 μmol/L berberine, as indicated by decreased CD206 fluorescence intensity in the berberine-treated co-culture group compared with the PTX model group (Figure 4A). These results suggest that berberine limits the acquisition of M2-associated characteristics in macrophages exposed to chemotherapy-induced apoptotic tumor cells (Figure 4).

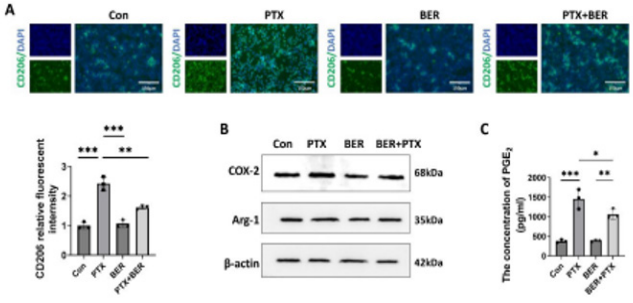


Figure 4: Berberine inhibits PTX-induced macrophage M2 polarization. (A) CD206 expression of receptor (THP-1) cells. (B) protein expression of feeder cells (COX-2) and receptor cells (Arg-1). (C) The PGE2 levels in supernatants. ** P<0.001.

Western blot analysis provided additional evidence of the effects of berberine on macrophage-associated signaling. COX-2 protein expression was elevated in PTX-treated SKOV3 feeder cells, whereas Arg-1 expression increased in recipient THP-1-derived macrophages. Berberine administration reduced the expression of both proteins within their respective cellular compartments, indicating attenuation of apoptosis-associated prostaglandin signaling and M2-related macrophage responses (Figure 4B).

To determine whether these molecular changes were accompanied by alterations in soluble inflammatory mediators, PGE2 concentrations were measured in the co-culture supernatants. PTX-induced apoptosis was associated with increased extracellular PGE2 production, whereas berberine supplementation significantly reduced PGE2 levels relative to the PTX model group (Figure 4C).

The concurrent reductions in CD206 and Arg-1 expression, COX-2 abundance, and PGE2 production suggest that berberine suppresses macrophage polarization responses associated with chemotherapy-induced tumor cell apoptosis. These observations identify the COX-2/PGE2 signaling axis as a potential mediator of the interaction between apoptotic ovarian cancer cells and macrophages, while indicating that berberine may interfere with the development of a tumor-supportive, M2-like macrophage phenotype.

COX-2 Overexpression Partially Reverses the Inhibitory Effect of Berberine on M2 Macrophage Polarization

Cyclooxygenase-2 (COX-2) is an important regulator of apoptosis-associated tumor repopulation, primarily through its involvement in prostaglandin E2 (PGE2) synthesis. Increased PGE2 production may also contribute to macrophage polarization toward the tumor-supportive M2 phenotype. To determine whether COX-2 participates in the inhibitory action of berberine, a COX-2 overexpression plasmid was introduced into the experimental co-culture system.

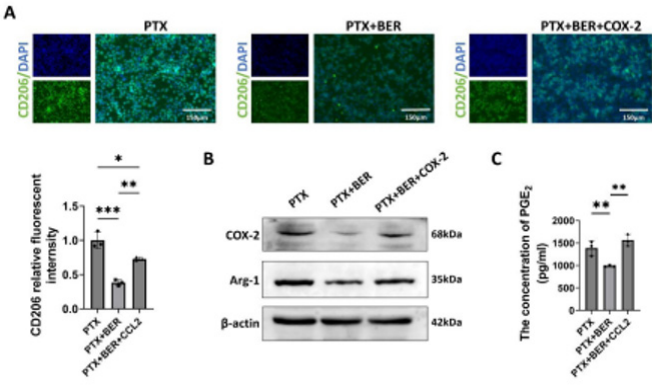


Figure 5: COX-2 reverses the inhibitory of berberine on M2 polarization of macrophages. (A) CD206 expression of receptor (THP-1) cells. (B) protein expression of feeder cells (COX-2) and receptor cells (Arg-1). (C) The PGE2 levels in supernatants. * P<0.001.

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Immunofluorescence analysis demonstrated that berberine reduced CD206 expression in macrophages exposed to paclitaxel (PTX)-induced apoptotic SKOV3 cells. However, forced COX-2 expression partially restored CD206 levels despite continued berberine treatment, suggesting that increased COX-2 activity could counteract the inhibitory effects of berberine on macrophage polarization (Figure 5).

A similar response was observed for arginase-1 (Arg-1), another protein associated with M2-like macrophage characteristics. Berberine administration decreased Arg-1 expression, whereas COX-2 overexpression increased its abundance relative to the berberine-treated group (Figure 5B). These findings indicate that the suppression of M2-associated markers by berberine is at least partly dependent on the regulation of COX-2-associated signaling (Figure 5A).

Further biochemical examination revealed that COX-2 overexpression increased PGE2 concentrations in the co-culture supernatants, reversing part of the reduction observed following berberine administration (Figure 5C). The parallel recovery of PGE2 production and M2-associated protein expression suggests a functional relationship between COX-2 signaling and macrophage phenotypic changes.

Taken together, these observations provide evidence that suppression of the COX-2/PGE2 pathway contributes to the ability of berberine to attenuate M2-like macrophage polarization induced by chemotherapy-associated tumor cell apoptosis.

Berberine Reduces Apoptosis-Associated Ovarian Tumor Repopulation

To investigate whether the inhibitory effects of berberine observed in cell culture could be reproduced in an animal model, a mouse xenograft model was established using a mixture of PTX-induced apoptotic ovarian cancer cells and untreated viable ovarian cancer cells. This experimental approach was designed to reproduce the growth-promoting influence of apoptotic tumor cells on surviving malignant populations.

Tumor growth measurements demonstrated that mice receiving a mixture of apoptotic and viable ID8 cells developed significantly larger tumors than animals in the control group inoculated with viable cells alone. In contrast, berberine administration substantially reduced tumor growth in mice exposed to the apoptosis-associated tumor microenvironment (Figure 6A and Supplementary Figure S1). These findings indicate that the presence of PTX-induced apoptotic cells enhanced tumor expansion, whereas berberine limited this response (Figure 6).

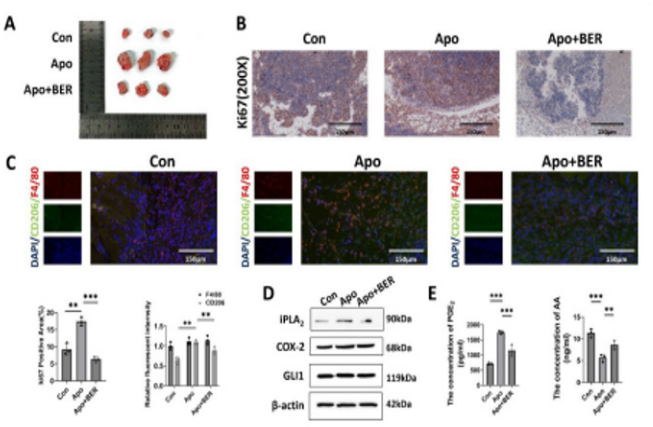


Figure 6: Berberine alleviates the repopulation of ovarian cancer in vivo. (A) Representative images of tumor tissues. (B) Ki67 expression in tumor tissue. (C) F4/80 and CD206 co-expression in tumor tissue. (D) protein expression in tumor tissue. (E) The AA and PGE2 levels in serum. ** P<0.001.

To further evaluate tumor proliferative activity, Ki67 expression was examined in tumor tissues. Immunohistochemical analysis revealed a pronounced increase in Ki67-positive cells in the apoptosis-associated group (Apo) compared with the control group. Berberine treatment reduced Ki67 expression, indicating decreased tumor cell proliferation following pharmacological intervention (Figure 6B).

The influence of berberine on macrophage polarization was subsequently assessed by examining the distribution of macrophages expressing F4/80 and CD206. Immunofluorescence analysis demonstrated an increased proportion of $F4/80^{+}CD206^{+}$ macrophages in tumors containing PTX-induced apoptotic cells. This population was reduced following berberine treatment, suggesting attenuation of M2-like macrophage polarization within the tumor microenvironment (Figure 6C).

These observations were consistent with the in vitro findings, supporting the possibility that berberine restricts apoptosis-associated tumor expansion while simultaneously reducing the accumulation of macrophages exhibiting tumor-supportive phenotypic characteristics.

To investigate the molecular mechanisms associated with these antitumor effects, the expression of proteins involved in AA metabolism and proliferative signaling was examined in tumor tissues. Increased levels of iPLA2, COX-2, and GLI1

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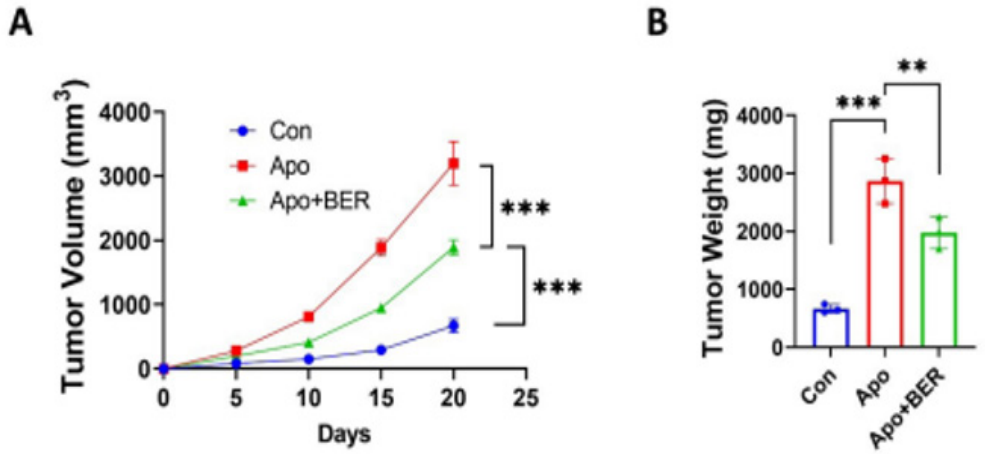


Figure S1: Berberine alleviates the repopulation of ovarian cancer in vivo. (A) Tumor growth curve. (B) Tumor weight. ** P<0.001.

were detected in tumors from the apoptosis-associated group, indicating activation of signaling components linked to prostaglandin synthesis and malignant cell proliferation. Berberine administration reduced the expression of these proteins, suggesting attenuation of the molecular responses induced by apoptotic ovarian cancer cells.

Additional biochemical measurements were performed to determine whether alterations in tissue protein expression were accompanied by changes in circulating AA and PGE2 concentrations. Serum analysis revealed that the apoptosis-associated tumor environment was characterized by increased PGE2 levels and reduced AA concentrations. Following berberine administration, PGE2 concentrations declined, whereas AA levels increased relative to the untreated apoptosis-associated group (Figure S1).

These results indicate that berberine suppresses tumor growth and M2-like macrophage polarization associated with PTX-induced ovarian cancer cell apoptosis in vivo. The accompanying reductions in iPLA2, COX-2, GLI1, and PGE2 support the involvement of altered AA metabolism and COX-2-dependent prostaglandin signaling in its antitumor activity. The findings also suggest that COX-2 represents an important molecular component through which berberine influences apoptosis-associated tumor repopulation and macrophage responses.

DISCUSSION

Despite considerable improvements in chemotherapy-based ovarian cancer management, disease recurrence and metastatic progression continue to limit sustained therapeutic responses [16]. Paclitaxel remains an important treatment option, particularly for advanced disease, because of its ability to interfere with microtubule dynamics and induce malignant cell death. Nevertheless, chemotherapy-induced apoptosis does not necessarily eliminate the biological influence of dying tumor cells. Instead, apoptotic populations may release molecular mediators that alter the surrounding microenvironment and support the proliferation of residual cancer cells. The present investigation provides experimental evidence that PTX-induced apoptotic ovarian cancer cells contribute to tumor repopulation through AA-associated signaling while simultaneously promoting macrophage polarization toward an M2-like phenotype. Importantly, berberine attenuated both responses, with the findings indicating that modulation of the COX-2/PGE2 signaling pathway contributes to these effects.

Chemotherapy-associated tumor repopulation represents a complex biological process in which signals generated during programmed cell death can unexpectedly facilitate the expansion of neighboring viable cells. This response, frequently described as the Phoenix Rising phenomenon, has been associated with the release of growth-promoting factors from apoptotic cells that stimulate residual malignant populations [17]. The present findings support this concept by demonstrating that PTX-treated SKOV3 feeder cells significantly enhanced the proliferative activity of untreated recipient SKOV3 cells. Increased Ki67 expression in the recipient population provided evidence of enhanced cell proliferation following exposure to soluble factors released from apoptotic feeder cells. These observations highlight the possibility that tumor cell elimination and tumor cell repopulation may occur simultaneously within a chemotherapy-exposed

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microenvironment.

The molecular analyses further suggest that caspase-3 activation contributes to the generation of signals that support residual ovarian cancer cell growth. Although caspase-3 primarily functions as an executioner of apoptosis, its activation may also initiate downstream biochemical events involving membrane phospholipid metabolism. In the present study, PTX exposure increased caspase-3 activation and was accompanied by elevated iPLA2 and COX-2 expression in apoptotic feeder cells. These changes occurred alongside reduced extracellular AA concentrations and increased PGE2 production, suggesting altered arachidonic acid utilization through prostaglandin-associated metabolic pathways. Increased GLI1 expression in surviving SKOV3 cells further indicated activation of signaling responses associated with malignant cell proliferation.

Berberine treatment diminished these chemotherapy-associated responses by reducing recipient cell proliferation and attenuating COX-2 and GLI1 expression. The accompanying decline in PGE2 production and partial recovery of AA concentrations suggest that berberine interferes with the metabolic signaling environment generated by apoptotic tumor cells. These findings support a potential role for the AA/COX-2/PGE2/GLI1 pathway in mediating the effects of berberine on apoptosis-associated ovarian cancer cell repopulation. However, the precise molecular interactions linking these signaling components require further investigation to establish their individual contributions and regulatory relationships.

Beyond the direct stimulation of surviving malignant cells, changes in the tumor microenvironment play a substantial role in the progression and recurrence of ovarian cancer. Tumor-associated macrophages are particularly influential because their functional characteristics can change in response to cytokines, chemokines, metabolic products, and other locally generated mediators. Macrophages exhibiting M2-like properties are frequently associated with immunosuppressive activity, extracellular matrix remodeling, angiogenesis, and the establishment of conditions favorable to tumor progression. Increased expression of CD206, CD163, and Arg-1 is commonly used to identify macrophage populations displaying these characteristics [18,19]. Although the tumor-promoting activities of M2-like macrophages have been widely investigated, the mechanisms connecting chemotherapy-induced tumor cell apoptosis with macrophage phenotypic changes remain incompletely understood [20].

The present findings suggest that apoptotic ovarian cancer cells actively influence macrophage behavior through soluble mediators generated following PTX exposure. In the Transwell co-culture system, THP-1-derived macrophages exposed to apoptotic SKOV3 cells exhibited increased expression of CD206, CD163, Arg-1, and TGF-β. These changes were accompanied by elevated COX-2 expression in feeder cells and increased PGE2 concentrations in the surrounding medium. The results suggest that prostaglandin-associated signaling may contribute to the development of an M2-like macrophage phenotype under chemotherapy-induced apoptotic conditions.

Berberine reduced the expression of macrophage markers associated with M2-like polarization and decreased PGE2 accumulation within the co-culture environment. Moreover, COX-2 overexpression partially restored CD206 and Arg-1 expression despite continued berberine exposure, providing additional evidence that COX-2-dependent signaling contributes to the observed macrophage responses. This partial reversal also indicates that COX-2 may not represent the only molecular pathway involved in berberine-mediated regulation of macrophage polarization.

The animal experiments strengthened the relevance of these observations by demonstrating that berberine reduced tumor growth, Ki67 expression, and the accumulation of $F4/80^{+}CD206^{+}$ macrophages in tumors containing apoptotic ovarian cancer cells. These changes were accompanied by reduced iPLA2, COX-2, and GLI1 expression, together with lower circulating PGE2 concentrations. The consistency between the cellular and animal findings suggests that modulation of AA-associated prostaglandin signaling may contribute to the ability of berberine to limit apoptosis-associated tumor expansion and macrophage polarization.

These findings identify berberine as a potential adjunctive compound for further investigation in ovarian cancer treatment. However, the evidence remains preclinical, and additional studies are necessary to establish its therapeutic effectiveness, optimal dosing, pharmacokinetic behavior, and long-term safety. Further experiments examining COX-2 inhibition, PGE2 receptor signaling, and macrophage-specific responses would also help clarify the mechanisms underlying the observed effects.

The results support the potential importance of simultaneously targeting tumor cell repopulation and tumor-supportive immune responses following chemotherapy. By attenuating COX-2-associated signaling,

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berberine may influence both the proliferative activity of surviving ovarian cancer cells and the development of an M2-like macrophage environment, providing a basis for future investigations into strategies designed to reduce chemotherapy-associated disease recurrence.

The present findings demonstrate that paclitaxel (PTX)-induced apoptosis in SKOV3 ovarian cancer cells is accompanied by increased prostaglandin E2 (PGE2) production, which may act as an important signaling mediator in promoting macrophage polarization toward an M2-like phenotype [21]. Cyclooxygenase-2 (COX-2), a key enzyme involved in PGE2 biosynthesis, appears to contribute to the molecular interactions linking chemotherapy-induced tumor cell death with changes in the tumor immune microenvironment. Berberine treatment substantially reduced COX-2 expression and was associated with decreased levels of M2-related macrophage markers, suggesting that its immunomodulatory activity is at least partly mediated through the regulation of prostaglandin signaling. To investigate the functional importance of COX-2, a rescue experiment was performed using a COX-2 overexpression plasmid. Forced expression of COX-2 partially counteracted the inhibitory effects of berberine, restoring PGE2 production and increasing the expression of macrophage polarization markers, including CD206 and arginase-1 (Arg-1). These findings provide experimental support for the involvement of COX-2 in apoptosis-associated macrophage responses and suggest that interference with the COX-2/PGE2 pathway represents an important component of berberine-mediated regulation of the tumor microenvironment.

To further examine the biological relevance of these observations, an in vivo tumor model was established by combining PTX-induced apoptotic ID8 ovarian cancer cells with untreated viable ID8 cells. This experimental design was intended to reproduce selected features of the residual tumor environment following chemotherapy, particularly the coexistence of dying malignant cells and surviving populations capable of continued proliferation. Consistent with the findings obtained from the cell-based experiments, berberine administration significantly restricted apoptosis-associated tumor growth in mice. This inhibitory response was supported by reduced tumor volumes and decreased Ki67 expression in tumor tissues, indicating suppression of malignant cell proliferation. Immunofluorescence analysis also revealed a reduction in $F4/80^{+}CD206^{+}$ macrophages following berberine treatment, suggesting attenuation of M2-like macrophage accumulation within the tumor environment. Furthermore, changes in prostaglandin-associated signaling were observed, including reduced PGE2 concentrations and decreased expression of proteins involved in AA metabolism and proliferative regulation. These results support the possibility that berberine influences both residual ovarian cancer cell expansion and macrophage-associated tumor-supportive responses through interconnected molecular mechanisms.

Beyond the experimental findings, berberine has attracted considerable interest as a naturally occurring isoquinoline alkaloid with a broad range of pharmacological activities. Its reported anti-inflammatory, metabolic, and anticancer properties have encouraged investigations into its potential application alongside conventional therapeutic agents. Previous studies have also described a comparatively favorable tolerability profile under certain experimental and clinical conditions, supporting continued interest in its therapeutic development [22,23]. However, favorable tolerability in specific settings does not establish its safety during prolonged administration at anticancer doses. This distinction is particularly important in ovarian cancer, where disease recurrence may develop after an extended interval following initial chemotherapy. Maintenance treatment strategies must therefore balance sustained therapeutic activity against cumulative toxicity and potential drug interactions. Although the biological properties of berberine make it an interesting candidate for further investigation, its suitability for long-term ovarian cancer maintenance therapy requires dedicated pharmacological and clinical evaluation [24,25].

Another important consideration is the reported ability of berberine to influence multiple biological pathways associated with malignant progression. Experimental evidence suggests that its anticancer effects may involve interference with cell proliferation, metabolic regulation, inflammatory signaling, and mechanisms contributing to treatment resistance [26,27]. These activities provide a rationale for exploring berberine in combination with established chemotherapeutic agents. In the context of PTX-based treatment, suppressing apoptosis-associated tumor repopulation may offer an additional therapeutic approach beyond the direct elimination of malignant cells. The present study demonstrates that berberine reduces the growth-promoting consequences of PTX-induced tumor cell apoptosis and attenuates M2-like macrophage polarization under the investigated experimental conditions. Previous research has also suggested that berberine may influence cancer cell sensitivity to chemotherapy, although the extent and mechanisms of these effects can vary across tumor models [23,27]. Consequently, further investigations

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are necessary to determine whether these responses translate into improved treatment efficacy, reduced chemoresistance, or sustained disease control in ovarian cancer patients.

Despite these encouraging observations, several challenges remain before berberine can be considered for clinical application in ovarian cancer treatment. One of the principal limitations is its restricted oral bioavailability, which has been attributed to poor gastrointestinal absorption, extensive metabolism, and transport-related barriers. These pharmacokinetic characteristics can limit systemic drug exposure and may reduce the amount of active compound reaching malignant tissues [28-30]. Such constraints are particularly relevant when attempting to reproduce the biological effects observed in cell culture and animal experiments under clinically achievable drug concentrations. Consequently, improving berberine delivery and tissue distribution represents an important consideration for future therapeutic development.

Nanotechnology-based drug delivery approaches have emerged as potential strategies for addressing the pharmacokinetic limitations of compounds with unfavorable absorption and distribution profiles. Nanocarrier systems may improve drug stability, modify release characteristics, and facilitate the simultaneous administration of therapeutic agents with complementary mechanisms of action. Previous experimental work involving a targeted nano delivery formulation containing berberine and doxorubicin demonstrated the feasibility of combining these compounds within a single carrier system [22]. The reported findings suggested improvements in drug delivery characteristics and combined antitumor activity, supporting further investigation of nanocarrier-based approaches for berberine administration. Nevertheless, improvements in oral absorption, systemic bioavailability, and tumor-selective accumulation must be established individually through appropriate pharmacokinetic and biodistribution studies.

Considering the central role of PTX in ovarian cancer chemotherapy and its association with apoptosis-driven tumor repopulation in the present experiments, developing a delivery system that incorporates both PTX and berberine may represent a worthwhile direction for future research. Such an approach could potentially combine the cytotoxic activity of PTX with the ability of berberine to attenuate COX-2-associated proliferative and immunomodulatory signaling. A carefully designed co-delivery platform might also provide opportunities to regulate drug release, coordinate exposure within tumor tissues, and reduce unwanted effects associated with conventional administration. However, the feasibility of this strategy remains to be established, and its potential advantages should not be assumed without direct experimental comparison.

Future investigations should therefore focus on developing and characterizing PTX–berberine co-delivery formulations, determining their physicochemical stability, evaluating drug-release behavior, and examining their pharmacokinetic and tissue-distribution profiles. Additional studies are needed to establish whether simultaneous or sequential administration provides greater therapeutic benefit, particularly because PTX-induced apoptosis and the subsequent production of growth-promoting mediators may occur at different stages of treatment. Evaluating these temporal relationships could help identify administration strategies that effectively limit apoptosis-associated signaling without compromising the cytotoxic effects of chemotherapy.

Further mechanistic experiments involving selective COX-2 inhibition, downstream PGE2 receptor modulation, and macrophage-specific signaling analyses would also help distinguish the direct effects of berberine on malignant cells from its indirect influence on immune populations. Such investigations could clarify whether COX-2 suppression is the principal mechanism responsible for the observed responses or one component of a broader network of berberine-sensitive pathways [26-30].

The present findings provide a foundation for examining therapeutic strategies that address the biological consequences of chemotherapy-induced tumor cell death. By reducing COX-2-associated PGE2 production, residual cancer cell proliferation, and M2-like macrophage polarization, berberine demonstrated activity against two processes potentially involved in ovarian tumor progression after chemotherapy. Improving its pharmacokinetic properties and establishing its effectiveness in more representative preclinical and clinical settings will be essential for determining whether these experimental observations can contribute to future approaches for preventing ovarian cancer recurrence.

CONCLUSION

The present study demonstrates that paclitaxel-induced apoptosis can promote ovarian cancer cell repopulation while encouraging macrophage polarization toward a tumor-supportive M2 phenotype. These responses were

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associated with activation of the caspase-3/iPLA2/AA/COX-2/PGE2 signaling pathway, increased proliferative activity, and alterations in the tumor microenvironment. Berberine effectively attenuated these chemotherapy-associated effects by reducing COX-2 expression, limiting PGE2 production, and suppressing M2-related macrophage markers. COX-2 overexpression partially restored macrophage polarization and PGE2 synthesis, further supporting the involvement of this pathway in berberine-mediated regulation. Consistent findings from animal experiments demonstrated reduced tumor growth, decreased Ki67 expression, and diminished M2-like macrophage accumulation following berberine administration. These observations suggest that berberine may provide a complementary approach to limiting apoptosis-driven tumor regeneration and associated immune alterations. However, its restricted bioavailability, potential pharmacological interactions, and uncertain long-term clinical effectiveness require further investigation. Future studies examining optimized delivery systems and combination strategies with paclitaxel may help establish its therapeutic relevance in ovarian cancer management.

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