



Research Article

The Potential Anti-Tumor Effect of CDK7 Inhibitor THZ2 in Preclinical Models of Ovarian Cancer

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Abstract

Cyclin-dependent kinase 7 (CDK7) is a CDK-activating kinase (CAK) complex component, including cyclin H and MAT1. CDK7 controls cell cycle progression and transcription by phosphorylating the carboxy-terminal domain (CTD) of RNA polymerase II (RNAPII), activating other CDKs, such as CDK1 and CDK2, and ensuring DNA replication. Inhibition of CDK7 prevents activation of other CDKs, thereby leading to apoptosis.

THZ2 is an analog of THZ1 with an improved half-life, a second-generation covalent inhibitor that exhibits high efficacy and selectivity in targeting cancer cells. As a highly selective covalent CDK7 inhibitor, THZ2 exhibits potent pan-cancer activity. However, the potential anticancer activities and mechanisms of THZ2 in ovarian cancer remain unidentified.

In this study, we demonstrate that THZ2 can markedly inhibit cell growth, arrest the cell cycle, and induce apoptosis, accompanied by dysregulation of several related proteins, including PARP, WEE1, XIAP, Mcl-1, BAX, p-CDK2, Cyclins, and p27. THZ2 also increases the intracellular ROS generation, which can be blocked by pretreatment with NAC. Additionally, NAC can partially rescue the THZ2-induced apoptosis. In conclusion, our investigations reveal novel therapeutic potential for the treatment of ovarian cancer.

Keywords: Ovarian cancer; THZ2; CDK7, CAK.

Introduction

Ovarian cancer is the second leading cause of death among gynecological cancers and one of the deadliest, with a low five-year survival rate compared to breast, uterine, vulvar, and endometrial cancers. It has been estimated that about 12,730 deaths from ovarian cancer will occur in 2025, with 20,890 new cases in the United States [1]. Despite extensive research on its underlying biology, ovarian cancer still lags behind cervical and breast cancers in five-year survival rates among gynecological cancer [2]. It is characterized by high heterogeneity, a low prevalence of common genetic alterations, and is often diagnosed at an advanced stage without specific clinical symptoms, frequently metastasizing to the abdomen [3]. Symptoms typically appear in late stages, resulting in poor prognoses and a high short-term mortality rate. Therefore, more research is needed to understand the key cancer-related events and develop new therapies that are highly effective and selective.

Disruption of cell cycle progression and abnormal regulation of cyclin-dependent kinases (CDKs) are recurring molecular findings in human cancers [4-6]. CDKs impact a variety of cellular processes, including cell cycle control, transcription, RNA processing, translation, neurogenesis, and apoptosis [7-9]. To date, 20 CDKs have been identified in mammals [10]. Some CDKs function as cell cycle regulators, others play vital roles in transcription, and some have yet to be assigned a clear function [11, 12]. Numerous studies have shown that CDK1, 2, 4, 6 govern the cell transition from quiescence to cell division [13, 16], whereas CDK7, [8, 9, 11, 12] induce the initiation, elongation of RNA processing, and splicing of RNA polymerase II (RNAP II) transcripts [8, 13]. However, unlike other CDKs, CDK7 has distinct and dual roles [14, 15]. At first, it performs as CDK-activating kinase (CAK) to promote phosphorylation of all CDKs [16-18], and on the other hand, it works as a subunit of TFIIF, a general transcription factor complex, to phosphorylate the carboxy-terminal domain (CTD) of RNAP II [19-21]. Numerous studies have reported that CDKs are involved in several essential steps of tumorigenesis and the development of cancer events [22, 23].

THZ1 is a highly selective covalent CDK7 inhibitor that effectively represses the phosphorylation of CDK7 substrates and exhibits broad antitumor efficacy [24]. Previous papers have

proven that THZ1 breaks the core transcriptional regulatory circuitry of CDK7 by targeting cysteine 312(C312) of CDK7 as an RNAP II kinase [25], and causes global mRNA downregulation in several transcriptionally addicted cancers, including T cell acute lymphoblastic leukemia, triple-negative breast cancer, small-cell lung cancer, and neuroblastoma [26]. In addition, THZ1 treatment induced cell cycle arrest, leading to decreased CAK activity, disrupted cell proliferation, and cell apoptosis [27]. However, recent studies have cited THZ1's short half-life and poor plasma pharmacokinetics as significant limitations for in vivo investigations, prompting the development of its analog, THZ2 [26]. Compared to THZ1, THZ2 has a significantly longer half-life (approximately 5-fold) and induces apoptotic cell death in various cancer cells, including gastric and triple-negative breast cancer cells, in vivo, by selectively binding to CDK7. Moreover, THZ2, administered at lower doses, efficiently suppressed TNBC cell growth in vitro [28, 29].

Using the cancer cell lines, in this study, we investigate the potential anticancer mechanisms of THZ2, an analog of THZ1 with improved pharmacokinetic properties and efficacy in preclinical models of ovarian cancer.

Materials and Methods

Cell culture, cell lines, and reagents

The human ovarian cancer cell lines A2780 (derived from untreated ovarian cancer patients, ovarian endometrioid adenocarcinoma, pathological features include: sensitive to cisplatin but can induce the development of resistant strains, e.g., A2780/CP70). OVCAR-3 (obtained from tumor tissue from patients with metastatic ovarian cancer and ascites from patients with ovarian serous cystadenocarcinoma) expresses CA125 (ovarian cancer marker) and the MDR1 gene (multidrug resistance gene). ES-2 (derived from tumor tissue of patients with ovarian clear cell carcinoma, highly invasive, with high levels of VEGF (vascular endothelial growth factor) expression). SKOV3 (from the ascites of ovarian adenocarcinoma patients, belonging to serous adenocarcinoma, with pathological features including TP53 gene mutation and low HER2/neu expression). HO8910 (established in ascites of Chinese ovarian cancer patients, the tumor morphology in nude mice is consistent with the original lesion. This cell line is suitable for studying various aspects of ovarian cancer cell proliferation, apoptosis, cell cycle, chemotherapy resistance, invasion, metastasis, and epithelial-mesenchymal transition (EMT),

commonly used in domestic laboratories. HO8910PM (cells are a highly metastatic subtype derived from HO-8910) were ordered from Shenhuishengwu (a cell company) and cultured in DMEM supplemented with 10% fetal bovine serum, streptomycin (100 µg/mL), and penicillin (100 U/mL) in a humidified incubator at 37°C and 5% CO₂. THZ2 was purchased from ApexBio Technology (A8717), and dihydroethidium (DHE) and N-acetyl-L-cysteine (NAC) were obtained from Sigma-Aldrich. Antibodies like Anti-GAPDH (KM9002) were from Tianjin Sungene Biotech., Anti-PARP (9542), Anti-p-CDK2 Thr160 (2561), Anti-BAX (2772) antibodies were ordered from Cell Signaling Technologies, Anti-XIAP (610762) and Anti-Cyclin E (51-1495GR) antibodies were available from BD Biosciences, Anti-Cyclin B1 (1169), Anti-CDK2 (0832) and Anti-Mcl-1 (2679) antibodies were bought from Ruiying Biological, Anti-Wee1 (5285), Anti-p27 (1641) and Anti-Bcl2 (492) antibodies were from Santa Cruz Biotechnology.

Cell Viability Assay

Cells were harvested and resuspended in a 96-well plate at a density of 4~6×10³ cells per well, and treated with drugs in three parallel wells for 72 h. Then 3-(4, 5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) was added to each well at a final concentration of 0.5mg/mL. After incubation for 4 hours, the formazan crystals were dissolved in 50µl of DMSO, and the absorbance at 570 nm was measured using a plate reader. The concentrations required to inhibit growth by 50% (IC₅₀) were calculated from survival curves using the Bliss method [31-33].

Apoptosis Assay

To assess cell apoptosis, a flow cytometry (FCM) assay was used. Following two PBS washes and cell harvesting, the cells were stained with Annexin V FITC and propidium iodide (PI) in binding buffer. After 15 minutes of dark incubation at room temperature, the cells were detected using FCM. Using the FL-1 (530 nm) and FL-2 (585 nm) filters, fluorescence was measured at excitation wavelengths of 480 nm (FL-1) and 585 nm (FL-2), respectively. The FlowJO software was used to quantify early apoptotic cells (Annexin V-positive only) and late apoptotic cells (Annexin V- and PI-positive) [34].

Cell Cycle Essay

Cells were seeded at a density of 3.0 × 10⁵ cells per well in 6-well plates and treated with THZ2. After 48 h cells were harvested and washed twice with cold PBS, then fixed with ice-cold 70% ethanol for 30 min at 4 °C. After centrifugation at 200 × g for 10 min, cells were washed twice with PBS and resuspended with 500 µl

PBS containing PI (50 µg/mL), DNase-free RNase (100 µg/mL) and Triton X-100 (0.1%), 0.1% sodium citrate, and detected by FCM after 15 min incubation at room temperature in the dark. Fluorescence was measured at an excitation wavelength of 480 nm through an FL-2 filter (585 nm). Data were analyzed using MoD Fit LT 3.0 software (Becton Dickinson).

Reactive Oxygen Species (ROS) Assay

Cells were pretreated with THZ2 for 48 h for the reactive oxygen species (ROS) assay and observed under a fluorescence microscope (Olympus, Japan) immediately after incubation with 10 µM DHE for 30 min at 37 °C in the dark. Five fields were randomly selected for each well [35]. ROS activation was analyzed by calculating the percentage of positive cells.

Western Blot Analysis

Cells were harvested and washed twice with cold PBS, then resuspended and lysed in RIPA buffer (1% NP-40, 0.1% SDS, 0.5% sodium deoxycholate, 10 ng/mL PMSF, 0.03% aprotinin, 1 µM sodium orthovanadate) at 4 °C for 30 min. After centrifugation at 14,000 × g for 10 minutes, the supernatants were collected and stored at -80 °C as whole-cell extracts. Total protein concentrations were determined with the Bradford assay. Proteins were separated on 12% SDS-PAGE gels and transferred to polyvinylidene difluoride membranes. Membranes were blocked with 5% BSA and incubated with the indicated primary antibodies. Corresponding horseradish peroxidase-conjugated secondary antibodies were used against each primary antibody. Proteins were detected using the chemiluminescent detection reagents and films.

Statistical Analysis

All results are expressed as mean ± standard deviation (SD). Statistical analysis of the differences between the two groups was performed with Student's t-test. A P-value <0.05 was considered a significant difference

Results

THZ2 inhibited the growth of ovarian cancer cells in vitro

To investigate the effect of THZ2 on ovarian cancer cells, six ovarian cancer cell lines (A2780, SKOV3, HO8910, HO8910 PM, OVCAR3, and ES2) were treated with increasing concentrations of THZ2 for 72 h, and DMSO was used as a control. As shown in Figures 1B and 1C, THZ2 exhibited a notable dose-dependent inhibition of ovarian cancer cell growth. Among the six cell lines, SKOV3 and A2780 cells showed the best sensitivity to THZ2, with IC₅₀ values of 0.1886 µM and 0.4683 µM, respectively.

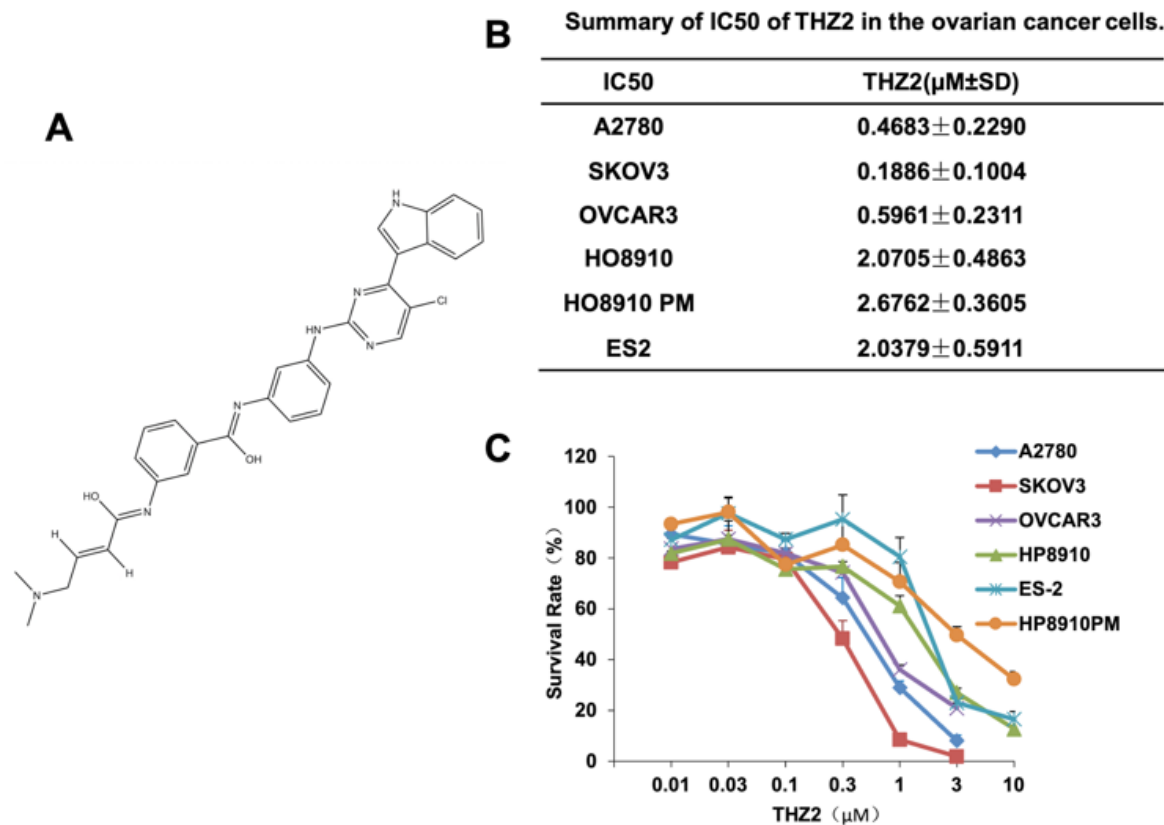


Figure 1: Ovarian cancer cells are shown. Cells were grown in 96-well plates for 24h and treated with the indicated concentrations of THZ2 for 72 h, and cell survival was examined by MTT assay. (C) Representative growth curves of cells treated with THZ2 showed inhibition of ovarian cancer cell growth in vitro. (A) Chemical structure of THZ2. (B) A summary of the IC 50 of THZ2 in the indicated THZ2 is shown. Data are mean $\pm$ SD o three independent experiments.

THZ2 promoted apoptosis in ovarian cancer cells in vitro

To determine whether the decreased survival of ovarian cancer cells induced by THZ2 is due to apoptosis, cell apoptosis is assessed by FCM with Annexin V/PI staining after THZ2 treatment. A2780 and SKOV3 cells were treated with the different concentrations of THZ2 (0.1, 0.3, and 1 μM) for 48h and stained with Annexin V/PI. As shown in Figure 2A and Figure 2B, THZ2 enhanced the early apoptosis (Annexin V+/PI-) and late apoptosis (Annexin V+/PI+) with the elevated THZ2 concentrations. Additionally, to further investigate the molecular mechanism of cell apoptosis, the levels of apoptotic-related proteins were analyzed by Western blot. As shown, THZ2 treatment dose-dependently increased cleaved PARP (C-PARP) expression, a classical apoptosis marker, in A2780 and SKOV3 cells (Figure 2C). Moreover, the protein levels of XIAP and Wee1 were significantly reduced in both cell lines. Our data demonstrate that THZ2 can activate several apoptosis pathways to varying degrees, thereby suppressing cell survival. THZ2 induced cell cycle arrest in ovarian cancer cells.

To determine whether the impact of THZ2 treatment on cell growth inhibition is also due to cell cycle arrest, cell cycle distribution is examined by FCM using PI staining. A2780 and SKOV3 cells were treated with THZ2 (0.1, 0.3, and 1 μ M) for 48h, stained with PI, and detected by FCM. The percentages of the sub-G1, G1/G0, S, and G2/M phases were calculated using the ModFit LT 3.0 software. Interestingly, THZ2 showed different effects on the enhanced S group accumulation, and reduced the G1/G0 population of SKOV3 cells at 1 μ M (Figure.3A and Figure.3B), accumulation of G2/M phase in A2780, which indicated that THZ2 induced cell cycle arrest at S phase in SKOV3, and at G2/M phase in A2780. As previously described, THZ2 was designed to bind CDK7 and covalently inhibit its phosphorylation activity. The protein levels of CDK7, p-CDK2, and CDK2 were analyzed by Western blot, along with cell cycle-related proteins, to uncover the mechanism of cell cycle arrest.

As shown in Figure 3C, THZ2 exposure resulted in a dose-dependent decrease in CCNB1, CCNE, and p27 in both ovarian cancer cells and suppressed the phosphorylation level of CDK2, with CDK2 and CDK7 remaining unchanged.

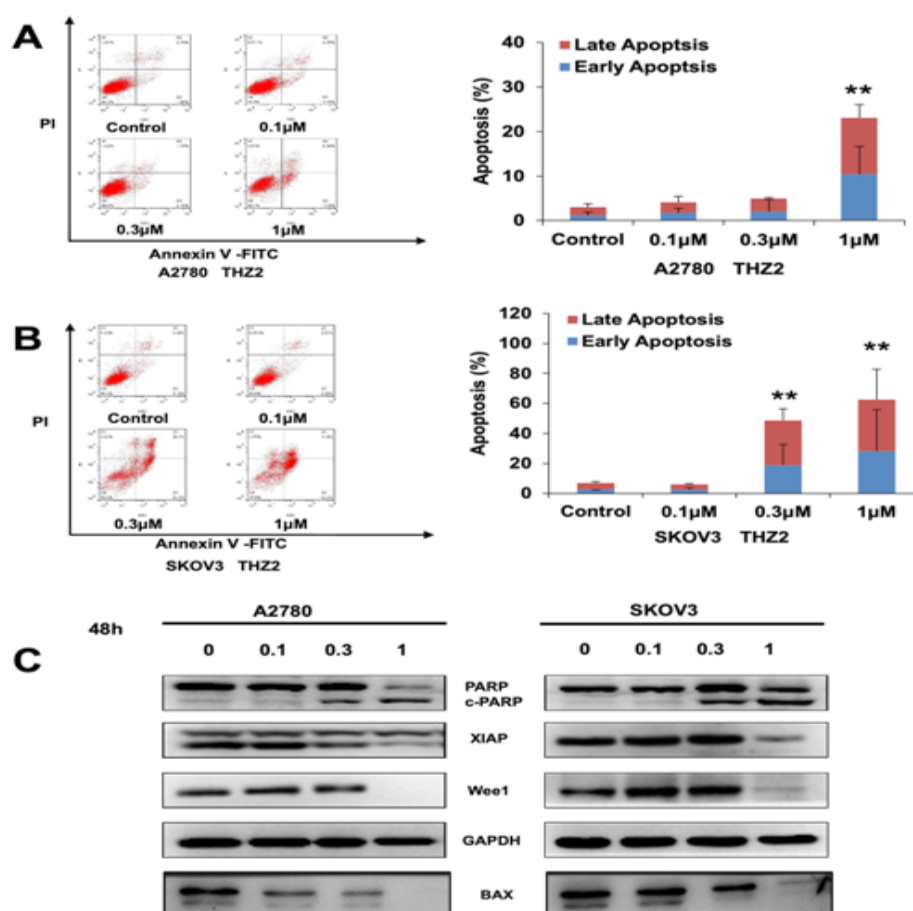


Figure 2: THZ2 promoted apoptosis in ovarian cancer cells in vitro. A2780 (A) and SKOV3 (B) cells were treated with THZ2 at the indicated concentrations. The apoptosis was detected by FCM Annexin V/PI staining. The proportions of Annexin V+/PI- and Annexin V+/PI+

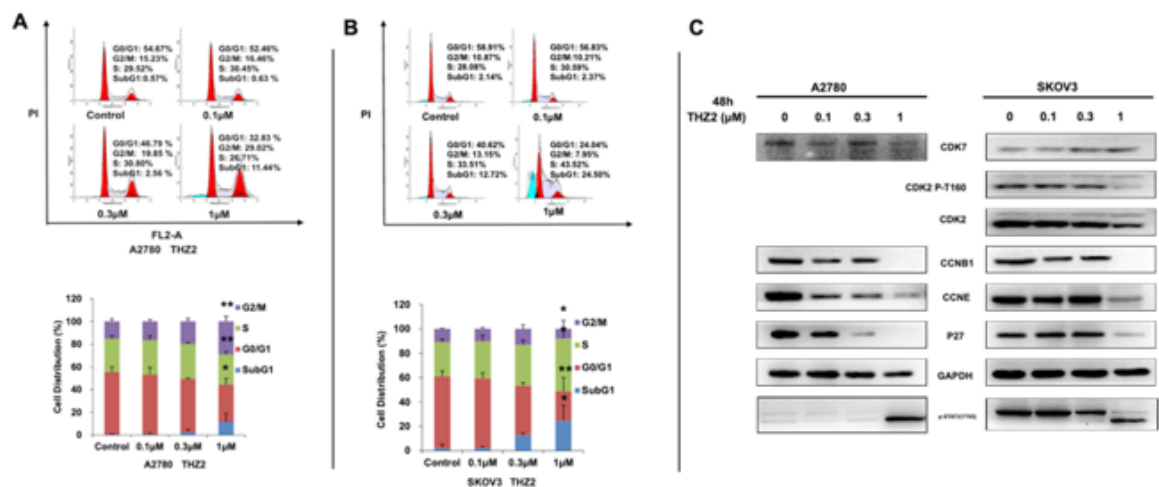


Figure 3: THZ2 induced cell cycle arrest in ovarian cancer cells in vitro. A2780 (A) and SKOV3 (B) cells were treated with THZ2 at the indicated concentrations. FCM detected the cell cycle distribution using PI staining. The percentages of subG1, G1G0, S, and G2/M phases were calculated using ModFit LT 3.0 software. Protein expression was examined by Western blot after cell lysis, and GAPDH was used as a loading control. Representative charts, quantified results, and Western blot results (C) from three independent experiments are shown. *P<0.05 and **P<0.01 vs. corresponding control.

THZ2 enhances ROS accumulation in ovarian cancer cells

Reactive oxidative species (ROS) are required for cancer initiation and, in turn, can be therapeutically exploited by overproducing ROS beyond intracellular limitations and initiating lethal chain reactions [34, 35]. To examine the role of ROS in the anticancer efficacy of THZ2 in ovarian cancer cells, we applied dihydroethidium (DHE), a ROS fluorescent probe, to stain cells treated with THZ2 for 48h. As shown in Figure 4A and Figure 4B, THZ2 enhanced the accumulation of ROS in both A2780 and SKOV3 cells in a dose-dependent manner, suggesting that THZ2 treatment can induce the generation of ROS in ovarian cancer cells.

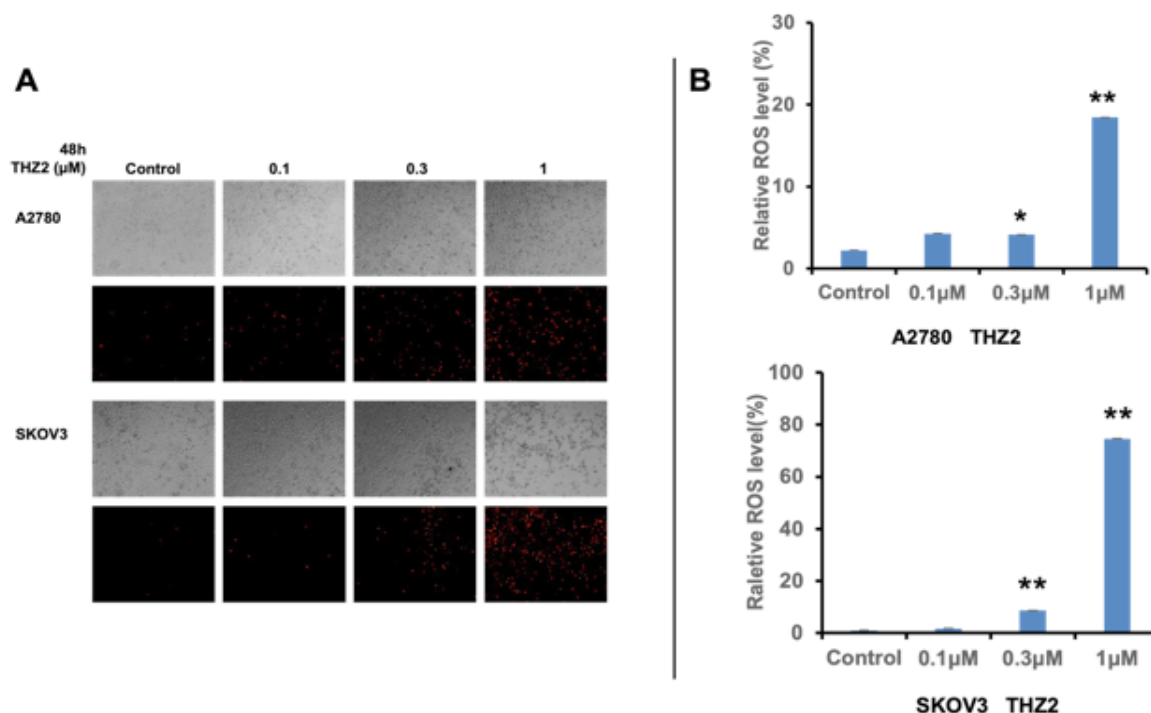


Figure 4: THZ2 enhanced ROS accumulation in ovarian cancer cells. A2780 and SKOV3 (A) cells were treated with THZ2 at the indicated times and concentrations, stained with DHE, and photographed under a fluorescent microscope. Representative micrographs and quantified results from three independent experiments are shown in (B). Statistical analysis of the difference between two groups is performed with Student's t-test. *P<0.05 and **P<0.01 vs. corresponding control.

ROS played a critical role in THZ2-induced apoptosis in ovarian cancer cells

As it is verified that ROS is accumulated by THZ2 in ovarian cancer cells, to further elucidate the potential

passageway of THZ2-induced apoptosis, which might be induced by ROS accumulation, A2780 and SKOV3 cells were treated with THZ2 at 1 μM for 48 h in the presence or absence of a 1 h pretreatment with the ROS scavenger NAC, and stained with DHE for fluorescence microscopy observation (Olympus, Japan). As shown in Figure 5A and Figure 5B, the DHE fluorescent signals induced by THZ2 were rescued by NAC in both cells. Additionally, both cells were stained with Annexin V and PI to assess apoptosis. NAC partially reversed the apoptosis in THZ2-treated A2780 and SKOV3 cells (Figure 5C). Our results indicate that THZ2 can result in ROS-dependent and independent apoptosis in ovarian cancer cells.

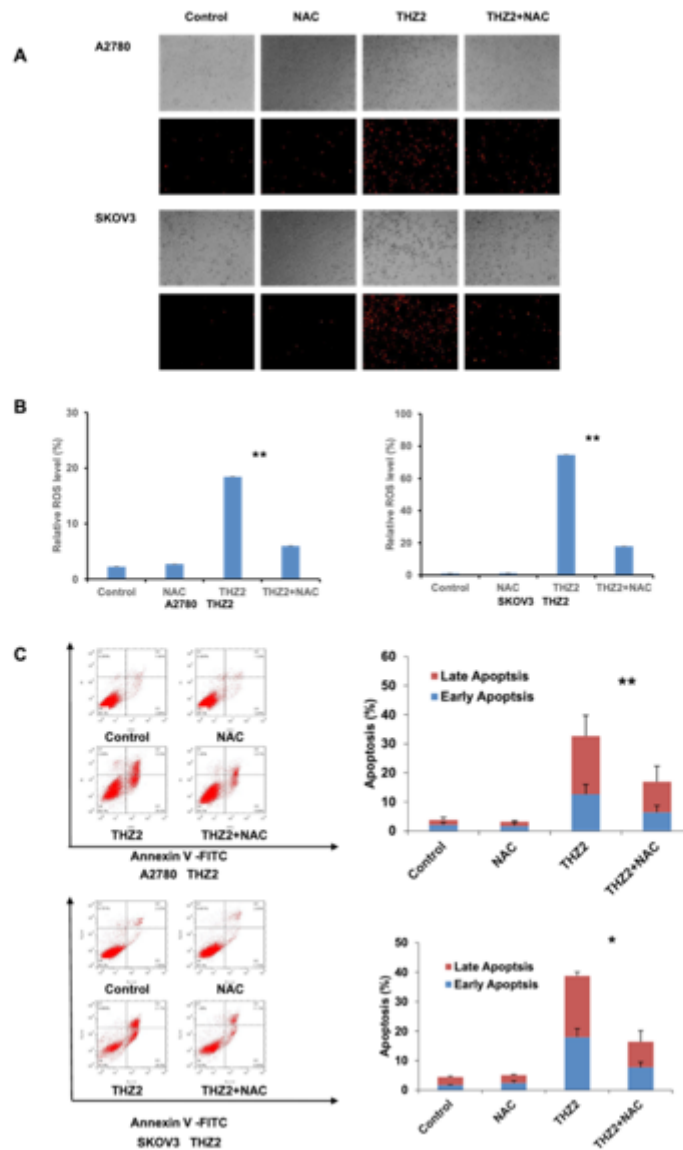


Figure 5: Inhibition of ROS partially rescued THZ2-induced apoptosis in ovarian cancer cells. A2780 and SKOV3 cells were treated with THZ2 at the indicated concentrations for 48h with or without the NAC (5 mM) pretreatment for 1 h, stained with DHE, and photographed under a fluorescent microscope (A). Apoptosis was detected by FCM using Annexin V/PI staining. The proportions of Annexin V+/PI- and Annexin V+/PI+ cells indicated apoptosis (C). Representative micrographs, charts, and quantified results from three independent experiments are shown. Statistical analysis of the difference between two groups is performed with Student's t-test. *P<0.05 and **P<0.01 vs. corresponding group.

Discussion

The diagnosis of epithelial ovarian cancer (EOC) is usually made in the advanced stage of the disease. EOC is associated with nonspecific signs, high intratumor heterogeneity, high recurrence rate, and therapy resistance. The International Federation of Gynecology and Obstetrics [FIGO] recommended cytoreductive surgery, together with multiple courses of chemotherapy, as the first-line therapy for advanced EOCs [30]; however, the majority of EOC patients may experience disease relapse or resistance within the first 3-5 years [31].

The radiochemistry of THZ1 was altered from 4-acrylamide-benzamide to 3-acrylamide-benzamide, leading to the development of THZ2, an analog of THZ1, which is a highly selective covalent CDK7 inhibition with diverse cancer-inhibitory effects, compared to the about 45minutes long in mouse plasma in vivo half-life of THZ1, THZ 2 is known to have five-fold increase half-life with improved pharmacokinetics in suppressing the growth of gastric and triple-negative breast cancer cells in vivo[24, 32]. However, currently, the role of THZ2 in ovarian cancer is still unclear.

Our study investigated the potential of THZ2 to inhibit the growth of ovarian cancer cells in vitro. In this study, our results show that THZ2 can remarkably mediate cell growth inhibition in several subtypes of ovarian cancer cells in a dose-dependent manner, triggering cell apoptosis with elevated cleaved PARP and decreasing XIAP, Wee1, Mcl-1, and BAX. THZ2 treatment for 48 hours resulted in a distinct G2/M cell cycle arrest in A2780 cells at 1 μ M and reduced the G1/G0 population in SKOV3 cells at the same concentration.

In the two ovarian cancer cell lines, A2780 and SKOV3, THZ2 treatment resulted in a distinct cell cycle distribution. This phenomenon may be rooted in different cell subtypes, accompanied by dose-dependent downregulation of CCNB1, CCNE, and p27, and decreased phosphorylation of CDK2, a CDK7 substrate. Moreover, THZ2 augmented intracellular ROS levels, and pretreatment with NAC partially scavenged ROS accumulation and partially reversed THZ2-induced apoptosis, indicating that THZ2 can initiate both ROS-dependent and independent apoptosis in ovarian cancer cells.

Focusing on protein expression following THZ2 treatment in ovarian cancer cells, we observed that THZ2 reduced CDK2 phosphorylation and inactivated the survival signaling pathway EGFR/Ras/AKT/ERK, as demonstrated in other cancers [33].

In their study, Baradács et al. found that the use of poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib, rucaparib, and niraparib in combination with platinum-based chemotherapy

improved the overall progression-free survival compared to chemotherapy alone in platinum-sensitive recurrent OC patients[34]. Although Parpisi are initially efficient and relatively tolerable, there is an increased chance of acquired resistance, leading to short-term relapse and survival among OC patients [35], thus highlighting the need for therapeutic sequencing and novel therapeutic research.

CDK7 is a reliable prognostic factor for ovarian cancer and has increasingly become a novel subject of interest among researchers. Cyclin-dependent kinase 7 (CDK7) promotes tumorigenesis and directly regulates transcription by phosphorylating cell cycle CDKs [15].

CDK7 inhibitors are molecules that specifically inhibit various enzymatic cofactors of the transcriptional machinery, which are promising therapeutic candidates. CDK7 inhibitors, such as THZ1, have been shown to induce cell cycle arrest, apoptosis, and transcriptional repression in various preclinical trial studies [36]. In their preclinical study, Zeng and colleagues found that the CDK7 inhibitor THZ1 significantly inhibited tumor cell growth in the ovarian cancer model [37]. THZ2, an analog of the first covalent inhibitor (THZ1) of CDK7, has been shown to have high efficacy and selectivity for inhibiting CDK7, CDK12, and CDK13, with a longer plasma half-life.

To summarize, all five ovarian cancer cell lines (A2780, SKOV3, OVCAR-3, HO8910, and HO8910 PM) exhibited reduced sensitivity to CDK7, resulting in global transcriptional downregulation, suppression of CDK7 substrate phosphorylation, including CDK2, and hindrance of downstream cell progression, including cell cycle and cell growth. THZ2 disrupted the balance that CDK7 maintains in the transcriptional machinery and blocked the activation of cyclin-dependent kinase-2. However, our understanding of the molecular determinants of THZ2 against ovarian cancer remains inadequate, revealing the genes with which THZ2 prefers to associate within ovarian cancer and necessitating further evaluation in the future. Moreover, our study was conducted in vitro; therefore, a preclinical in vivo study is needed to maximize the research's impact.

To conclude, our study provides strong evidence that THZ2 suppresses cell growth by inducing cell cycle arrest and apoptosis, disrupts the transcription program by targeting CDK7, and has the potential for an anti-tumor effect in preclinical models of ovarian cancer. THZ2 could serve as a promising therapeutic option for ovarian cancer control.

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Credit Authorship Contribution Statement

L. H. conducted the experiment and drafted the manuscript. X. H., J. H., Y. S., M.W., Z. S., and Z.S. participated in the data collection, data analysis, and ultrasound analysis and contributed to the manuscript. X. Y. conducted the critical revision of the manuscript. The final version of the manuscript was submitted with the approval of all authors.

Data Availability

Data is available upon request.

Funding Statement

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Ethics approval and consent to participate

The Ethics Committee approved the present study protocol for Clinical Research in accordance with the First Affiliated Hospital of Wenzhou Medical University. Research methods were carried out in accordance with relevant guidelines and regulations (the Helsinki Declaration).

Declaration of conflict of interest

The authors declare that they have no conflict of interest

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