

ORIGINAL ARTICLE

Role of inhibitor of yes-associated protein 1 in triple-negative breast cancer with taxol-based chemoresistance

Ying Li¹ | Shunan Wang² | Xi Wei³  | Sheng Zhang¹ | Zian Song¹ | Xiao Chen¹ | Jin Zhang¹

¹The Third Surgical Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy of Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China

²Department of Radiology, Daping Hospital, Army Medical University, Chongqing, China

³Department of Diagnostic and Therapeutic Ultrasonography, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China

Correspondence

Jin Zhang, The Third Surgical Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy of Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China.
Email: zhangjin@tjmuch.com

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Triple-negative breast cancer (TNBC) is highly clinically aggressive and taxol-based chemoresistance remains a big TNBC therapeutic problem to be solved. Verteporfin, a small molecular yes-associated protein 1 (YAP1) inhibitor, is little known as an anti-tumor drug for TNBC. Our data showed that YAP1 expression was associated with early relapse in tissue samples of patients with TNBC taxol chemoresistance ($P < .001$). Verteporfin reduced migration and enhanced apoptosis or autophagy of a taxol-resistant MDA-MB-231 cell line in vitro. Knockdown of YAP1 increased epithelial-mesenchymal transition response in a taxol-resistant TNBC cell line. In an in vivo experiment, we found that verteporfin was able to shrink tumor weight and volume and decreased Ki67 expression in a taxol-resistant mouse model. Our results provide evidence that verteporfin could be a chemosensitizer for TNBC patients with taxol-based treatment.

KEYWORDS

chemoresistance, inhibitor, taxol, triple-negative breast cancer, YAP1

1 | INTRODUCTION

Breast cancer is rated the number one cancer in new cancer cases and deaths reported in China since 2015.¹ Breast cancer is increasingly recognized as a heterogeneous disease. The highly diverse tumor types often associate with disease progression, treatment, and prognosis. Triple-negative breast cancer (TNBC)

is a breast cancer subtype characterized by lack of expression of steroid hormone receptors (HR), such as estrogen receptor (ER) and progesterone receptor (PgR), as well as ErbB-2/human epidermal growth factor receptor 2 (HER-2). TNBC accounts for 15%-20% of all breast cancer cases.² Clinical and pathological features of TNBC are associated with younger women, aggressive behavior, early relapse and poor prognosis. Due to lack

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of ER and Her-2 expression in TNBC, endocrine and Herceptin (Trastuzumab, Genentech Inc., South San Francisco, CA, USA) therapies are not considered primary treatment and adjuvant chemotherapy such as anthracycline- and taxol-based regimens remain the mainstream treatment.

The majority of TNBC expresses a “basal-like” molecular gene profile, and the BRCA1 pathway contributes to sporadic basal-like breast cancer. To date, tumors respond initially to chemotherapy and targeted agents, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and poly (ADP-ribose) polymerase (PARP) inhibitors, but there is poor overall survival (OS) of TNBC mainly due to drug acquired resistance.³ In TNBC treatment, taxol-based regimens have proven to be an important chemotherapy agent. Taxol induces mitosis arrest by stabilizing the spindle microtubules responsible for segregation of duplicated chromosomes to daughter cells. However, the utility of taxol-based chemotherapy in TNBC is limited by the development of drug resistance.

The yes-associated protein (YAP) is inhibited in the Hippo pathway which is a highly conserved cascade from yeast to humans. YAP1, a member of the YAP family, is a transcriptional co-activator that regulates transcriptional enhancer activator domain (TEAD) transcription factors and promotes cell proliferation.⁴⁻⁷ Several studies have shown overexpression of YAP 1 in human cancers.^{6,8-10} Accumulating evidence has suggested oncogenic roles of YAP in cancer progression.⁸ Thus, development of pharmacological inhibitors of YAP activity could be potentially valuable in anticancer therapy. Verteporfin (VP) is a small molecular YAP1 inhibitor that disrupts YAP1 conformation and its TEAD-YAP complex. Verteporfin has strong inhibitory effects on cancer cell growth and proliferation. However, the biological significance of anti-YAP therapy in TNBC with taxol chemoresistance is still unclear. In the current study, we reported that YAP1 overexpression is associated with early relapse in TNBC patients, suggesting a potentially significant role of YAP1 in chemoresistance TNBC. We aimed to investigate the functional role of verteporfin in TNBC with taxol resistance in a cell culture system and in an animal model.

2 | PATIENTS AND METHODS

2.1 | Patient information

One hundred patients were diagnosed with TNBC and treated with taxol-based chemotherapy for at least six cycles between 2013 and 2015 at Tianjin Medical University Cancer Institute and Hospital and at Daping Hospital in Chongqing. Average age was 61.8 years (range 17-89 years). Time of recurrence ranged from 1 month to 94 months and median time was 19 months. Median follow-up time for TNBC was 71 months. Evaluation of the clinical cases was approved by both Tianjin Medical University Institutional and Daping Hospital Review Board. All human tumor tissues were obtained with written informed consent prior to participation in the study.

2.2 | Cell culture and reagents

Human breast cancer cell line MDA-MB-231 (TNBC, purchased from China Center for Type Culture Collection, CCTCC, Wuhan, China) was cultured in DMEM medium supplemented with 10% FBS, 1% penicillin and streptomycin, 1% non-essential amino acids, 1% sodium pyruvate, and grown in a humidified incubator at 37°C with 5% CO₂. Verteporfin (1 μmol/L, purchased from MedChemExpress corporation, Shanghai, China) was used to treat cells in culture. All tissue culture reagents were purchased from Sigma-Aldrich (St Louis, MO, USA).

2.3 | Plasmid, siRNA and transfection

YAP1 Trilencer-27 siRNA was purchased from Ribbio Company, Shanghai, China and siRNA transfection reagent was purchased from Santa Cruz Biotechnology (Dallas, TX, USA). Three si-YAP1 RNA sequences were as follows: 1: 5'-GCGTAGCCAGTTACCAACA-3'; 2: 5'-CAGTGGCACCTACTCT-3'; 3: 5'-GGTGATACTATCAACCAA-3'. Cells were inoculated in a six-well plate overnight and transfected or treated when reaching 30% confluence. Efficiency of YAP1 siRNAs was determined 72 hours post-transfection according to the manufacturer's instructions.

2.4 | Tissue RNA isolation

Paraffin-embedded tissue samples were cut into 5-10-mm thickness sheets. Total RNA was extracted from the tissue sheets (2-8 sheets) following the manufacturer's instructions (Bioteck Corporation, Beijing, China).

2.5 | Taxol-resistant cell line (MDA-MB-231-TAXO)

MDA-MB-231 cell line was collected and treated with taxol for 4-5 months. IC₅₀ was analyzed to record cell viability under taxol treatment. The final taxol-resistant fold was calculated by the IC₅₀ of MDA-MB-231-TAXO/MDA-MB-231. The entire process followed the manufacturer's instructions (Rui Er Kang Corporation, Beijing, China).

2.6 | Animal transplantation tumor experiment

MDA-MB-231 taxol resistance cell line (231R) and 231R stably expressing vector-only and YAP1 shRNA were suspended in PBS solution, and cell count was adjusted to 1 × 10⁷/mL. During every 4 to 6 weeks, nude mice were injected with 100 μL cell suspension. Then, 1 week after each injection, tumor growth was monitored. When tumor volume reached 100 mm³ (calculated using the formula $v_{\text{tumor}} = \frac{1}{2} \times a \times b^2 \times \pi/6$; b is the length and a is the width in mm), tumor sizes were recorded weekly to control tumor volume within 1500 mm³. Verteporfin was i.p. injected (5 mg/kg body weight) every 2 days for 3 weeks, and the control group was injected with an equal volume of PBS. Tumor volume was measured using magnetic resonance

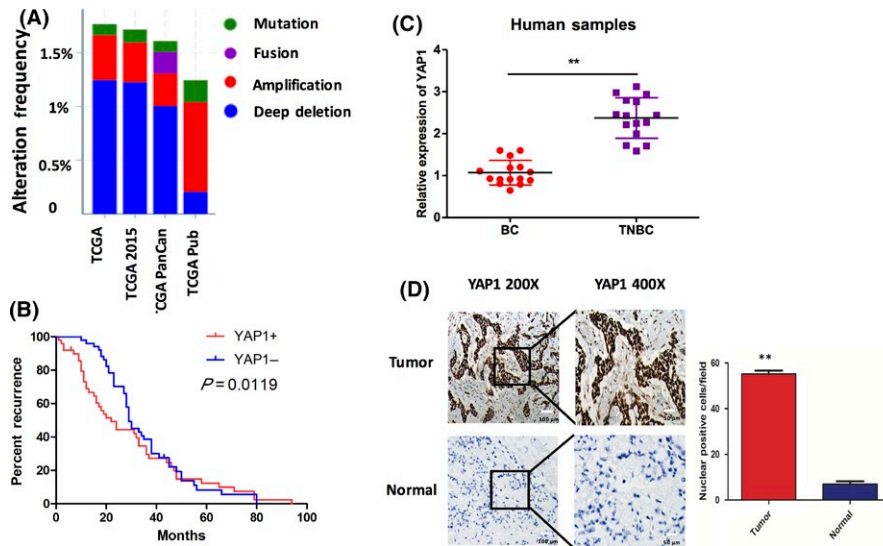


FIGURE 1 Yes-associated protein 1 (YAP1) expression in triple-negative breast cancer (TNBC) patient samples with taxol-based therapy. A, Alterations (amplification, fusion, mutation and deep deletion) of YAP1 gene in a subset of breast cancers from The Cancer Genome Atlas (TCGA) database (data from CBio website). B, Kaplan-Meier curve was analyzed in the correlation between YAP1 expression and tumor recurrence rate of patients with TNBC. C, Comparison of YAP1 mRNA levels from TNBC and non-TNBC paraffin-embedded tumor samples (N = 15 per group). D, Representative images of immunohistochemistry of YAP1 expression in tumor tissue and pericarcinoma tissue from TNBC patients (N = 200 per group). Scale bars, 100 μm and 50 μm . Data are represented as mean and SEM from three independent experiments. $**P < .01$

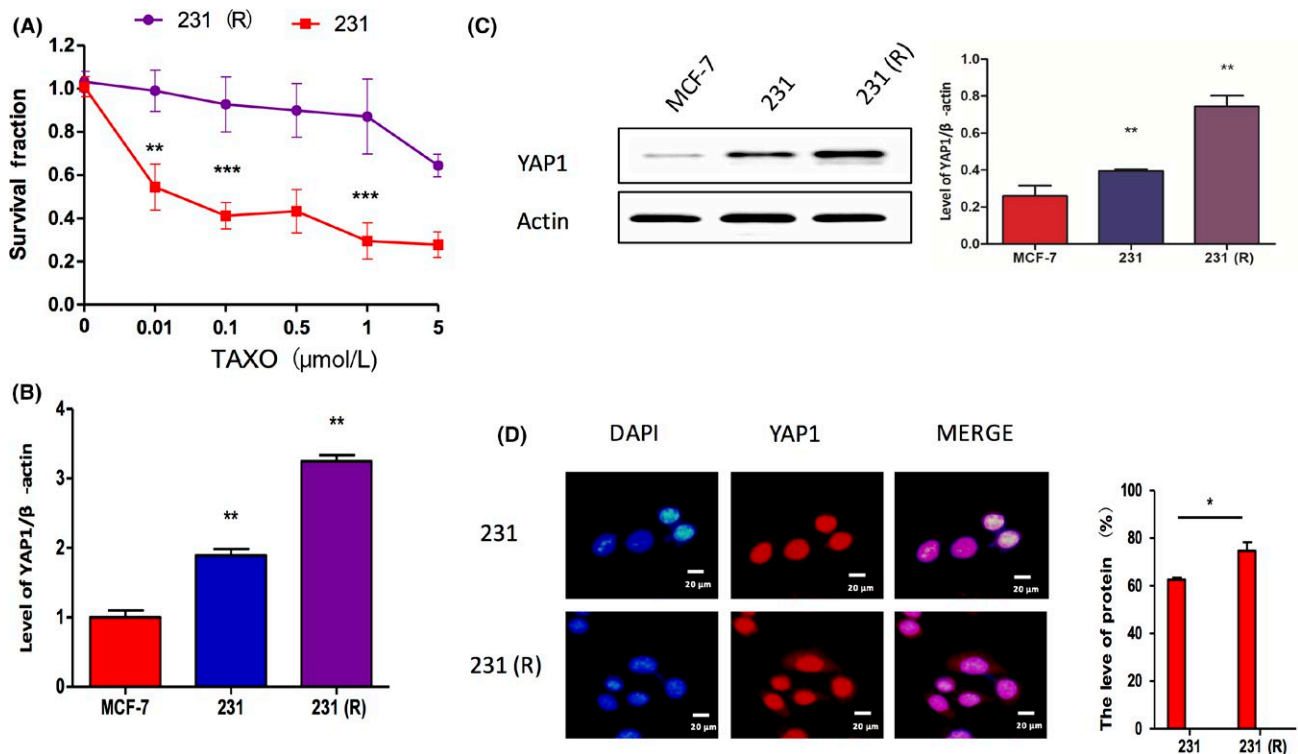


FIGURE 2 Yes-associated protein 1 (YAP1) expression in MDA-MB-231 and taxol-resistant cells in vitro. A, Cell viability assay (CCK-8 assay) was used to quantify cell proliferation in MDA-MB-231 and MDA-MB-231 taxol-resistant cell (231 R) groups. RNA and protein levels of YAP1 were analyzed in MCF-7, MDA-MB-231 and MDA-MB-231 taxol-resistant cell lines by RT-PCR (B), western blot (C) and cell immunofluorescence assay (D). Scale bars, 20 μm . Data are represented as mean and SEM from three independent experiments. $*P < .05$. $**P < .01$. $***P < .001$

imaging (MRI; 7.0-T MRI; Bruker Biospec 70/20USR, Ettlingen, Germany) every week. Transplanted tumor was harvested at the end of the experiments. All animal experiments were approved by the Animal Care Committee of Tianjin Medical University.

Immunohistochemistry, western blotting, antibodies and reagents, cell viability assay, quantitative real-time PCR, cell immunofluorescence assay and cell apoptosis assay was carried out as described in supplemental materials. Additional materials and methods can be found in Document S1.

2.7 | Statistical analysis

Data were analyzed and the significance between groups of treatments determined by Student's *t* test, χ^2 test, or Pearson correlation test with SPSS 22.0 software. Progression time (or confirmed relapse), or the end of follow up were calculated. Kaplan-Meier survival curves were constructed, and between-group differences were tested using both log-rank and Gehan-Breslow-Wilcoxon test; and $P \leq .05$ was considered significant.

3 | RESULTS

3.1 | Yes-associated protein 1 expression in TNBC patients with taxol-based resistance

Based on The Cancer Genome Atlas (TCGA) data (<http://www.cbioportal.org>) for patients with "breast cancer" (TCGA, TCGA

2015, TCGA PanCan and TCGA Pub) on the CBio website, amplification and deep deletion of the YAP1 gene was found in a subset of breast cancer patients (Figure 1A). To investigate YAP1 expression in TNBC patients with taxol-based resistance, we selected 100 patients with TNBC who underwent six cycles of taxol-based chemotherapy from 2009 to 2013 at Tianjin Cancer Hospital. We examined correlation of YAP1 gene status with time of recurrence in TNBC patients after the treatments. Results suggested YAP1 overexpression was associated with early relapse in TNBC patients after taxol-based chemotherapy ($P = .0119$, Gehan-Breslow-Wilcoxon test) (Figure 1B). Furthermore, qPCR analysis showed a significantly higher level of YAP1 gene expression in TNBC patients than in non-TNBC patients ($P < .0001$) (Figure 1C). This result was confirmed in an immunohistochemistry (IHC) study where 200 TNBC tissues along with matched controls were subjected to IHC staining for YAP1. Results showed increased nuclear YAP1 staining compared to normal tissues ($P < .0001$) (representative staining shown in Figure 1D). Together, the data showed that YAP1 was upregulated in TNBC patients and associated with earlier relapse following taxol-based treatment.

3.2 | Upregulation of YAP1 in TNBC cells with taxol resistance in cell culture

In the in vitro experiment, we first established the MDA-MB-231 taxol-resistant cell line (231R, 9.2-fold) and this cell line was then tested in the in vitro experiment (Figure 2A). Next, we investigated

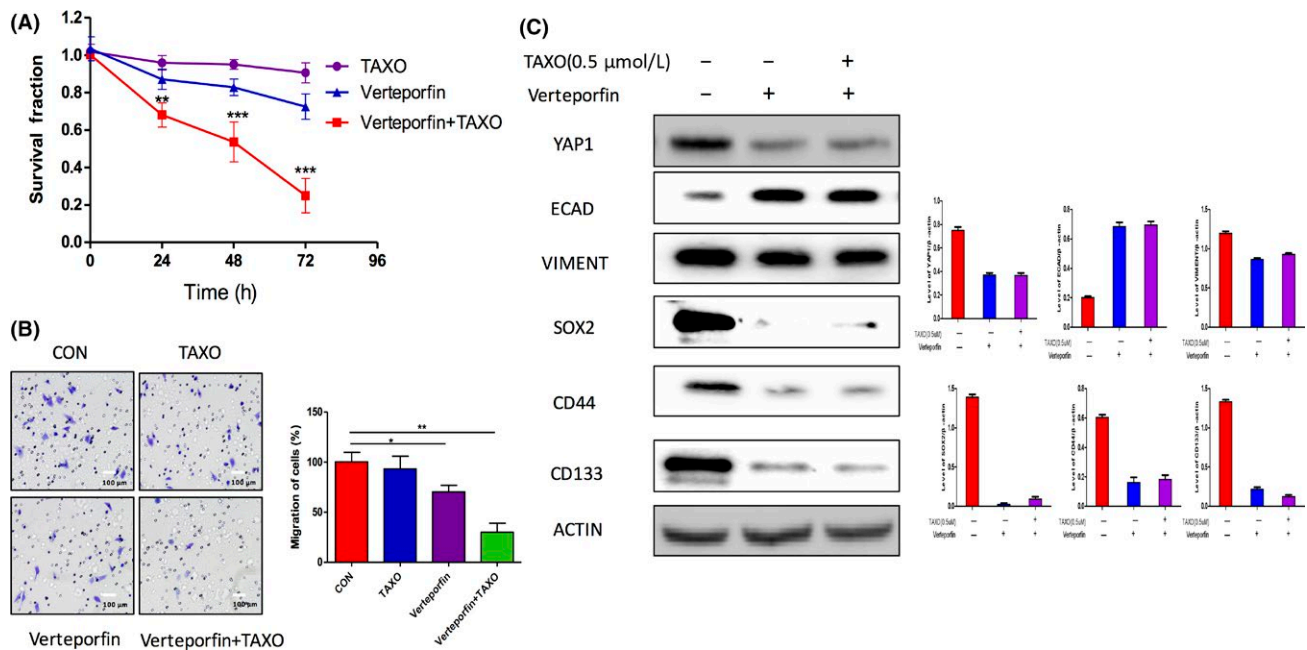


FIGURE 3 Verteporfin regulates cell migration and autophagy in triple-negative breast cancer (TNBC) with taxol resistance in vitro. A, Cell viability assay (CCK-8 assay) was used to quantify cell proliferation in 231-taxol resistance, verteporfin and verteporfin + 231-taxol resistance groups. B, Cell migration was detected by Transwell migration assay in control, 231-taxol resistance, verteporfin and verteporfin + 231-taxol resistance groups. C, Yes-associated protein 1 (YAP1), E-cadherin, vimentin (epithelial-mesenchymal transition [EMT] pathway), SOX2 CD44 and CD133 (autophagy markers) were detected by western blot in control, verteporfin (1 μmol/L) and verteporfin + 231-taxol (0.5 μmol/L) resistance groups. Scale bars, 100 μm. Data are presented as mean and SEM from three independent experiments. * $P < .05$. ** $P < .01$. *** $P < .001$

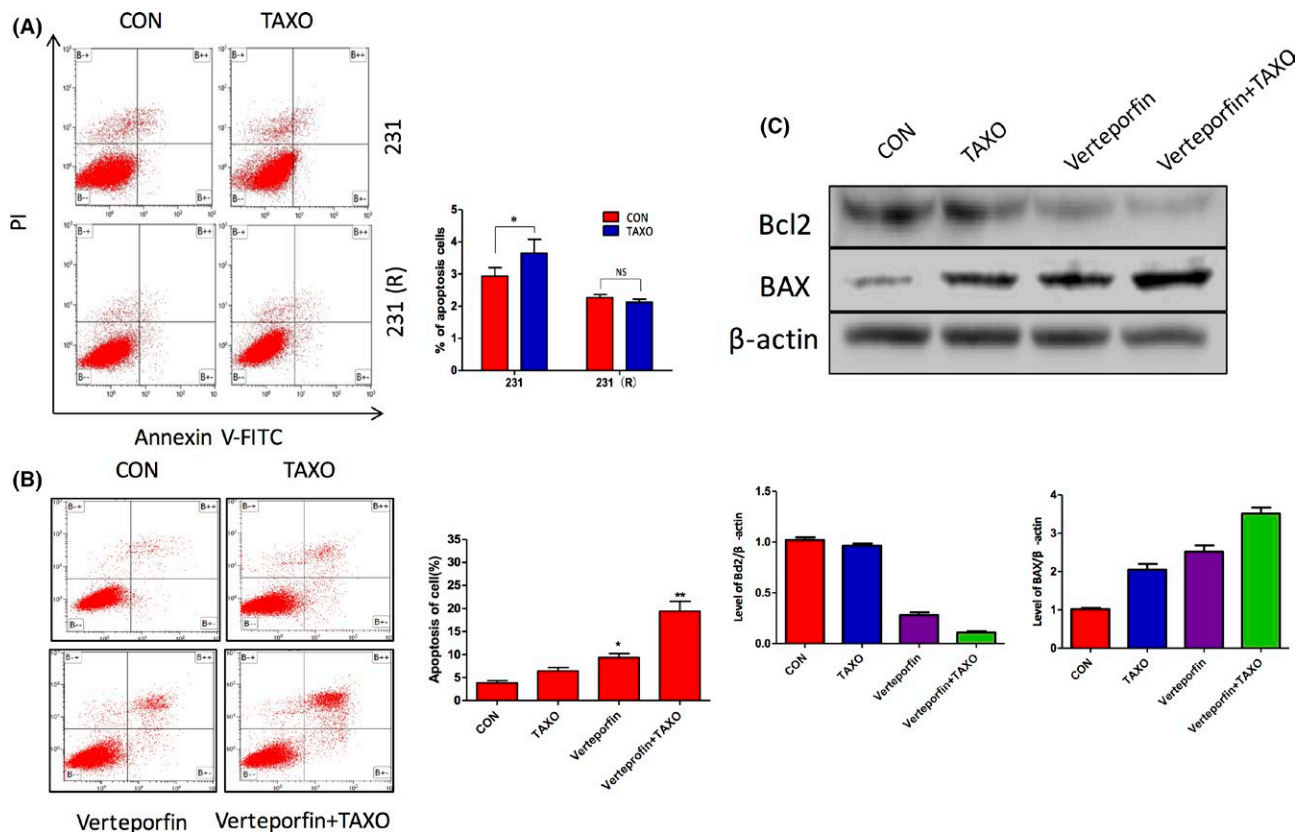


FIGURE 4 Verteporfin enhances cell apoptosis in triple-negative breast cancer (TNBC) with taxol resistance. A, Cell apoptosis rate was measured by flow cytometry and apoptosis assay in MDA-MB-231 and MDA-MB-231 taxol-resistant cells (231 R). B, Cell apoptosis rate was measured by flow cytometry and apoptosis assay in control, 231-taxol resistance, verteporfin and verteporfin + 231-taxol resistance groups. C, Bcl2 and BAX expression were detected by western blot in control, verteporfin (1 $\mu\text{mol/L}$) and verteporfin + 231-taxol (0.5 $\mu\text{mol/L}$) resistance groups. Data are presented as mean and SEM from three independent experiments. * $P < .05$. ** $P < .01$. NS, not significant

RNA and protein level of YAP1 in MCF7, MDA-MB-231 and MDA-MB-231/taxol in vitro. YAP1 was overexpressed in MDA-MB-231 with taxol resistance compared with two other breast cancer cell lines ($P < .0001$) (Figure 2B-D, Figure S1A). These data suggested that YAP1 was upregulated in TNBC with taxol resistance in vitro.

3.3 | Verteporfin regulates cell migration and autophagy in TNBC with taxol resistance

Verteporfin, a small molecule inhibitor of YAP1, was used in the MDA-MB-231 taxol resistance (231R) in vitro study. Survival rate was higher in MDA-MB-231 than in MDA-MB-231/taxo cells ($P < .0001$) (Figure 3A). High inhibition of migration and survival of MDA-MB-231 cells was seen in verteporfin + taxol cells when incubated with taxol, verteporfin or a combination of verteporfin and taxol (Figure 3B). Similar phenotype of migration inhibition was also observed after knockdown of YAP1 protein (Figure S1B). In addition, verteporfin or YAP1 siRNA decreased SOX2, CD44 and CD133 expression of autophagy and enhanced E-cadherin and vimentin expression in the epithelial-mesenchymal transition (EMT) pathway (Figure 3C, Figure S2A,B). However, after overexpressing YAP1 protein in 231R cells, we observed decreased E-cadherin and increased CD133 expression but this phenotype was partially reversed after verteporfin treatment

(Figure S3A). Taken together, verteporfin may inhibit the migration of TNBC cells and regulate autophagy or EMT of TNBC in vitro.

3.4 | Yes-associated protein 1 inhibitor enhances apoptosis in TNBC with taxol resistance in vitro

To investigate the effect of verteporfin treatment on MDA-MB-231 taxol resistance in vitro, we studied TNBC taxol-resistant cells treated with verteporfin. Apoptosis rate was significantly higher in MDA-MB-231/taxo after verteporfin and YAP1 siRNA treatment ($P < .0001$) (Figure 4A,B). Moreover, expression of Bcl2 was inhibited and that of Bax was increased in the verteporfin treatment group (Figure 4C). In the in vitro experiment, we also observed decreased BAX and increased Bcl2 expression after knocking down YAP1 protein in 231 R cells (Figure S3B). Therefore, verteporfin, the YAP1 inhibitor, significantly enhances apoptosis of TNBC with taxol treatment resistance in vitro.

3.5 | Verteporfin sensitizes taxol treatment of TNBC in vivo

Our observations that the YAP1 inhibitor verteporfin enhanced the apoptosis of taxol-resistant TNBC cells encouraged our further

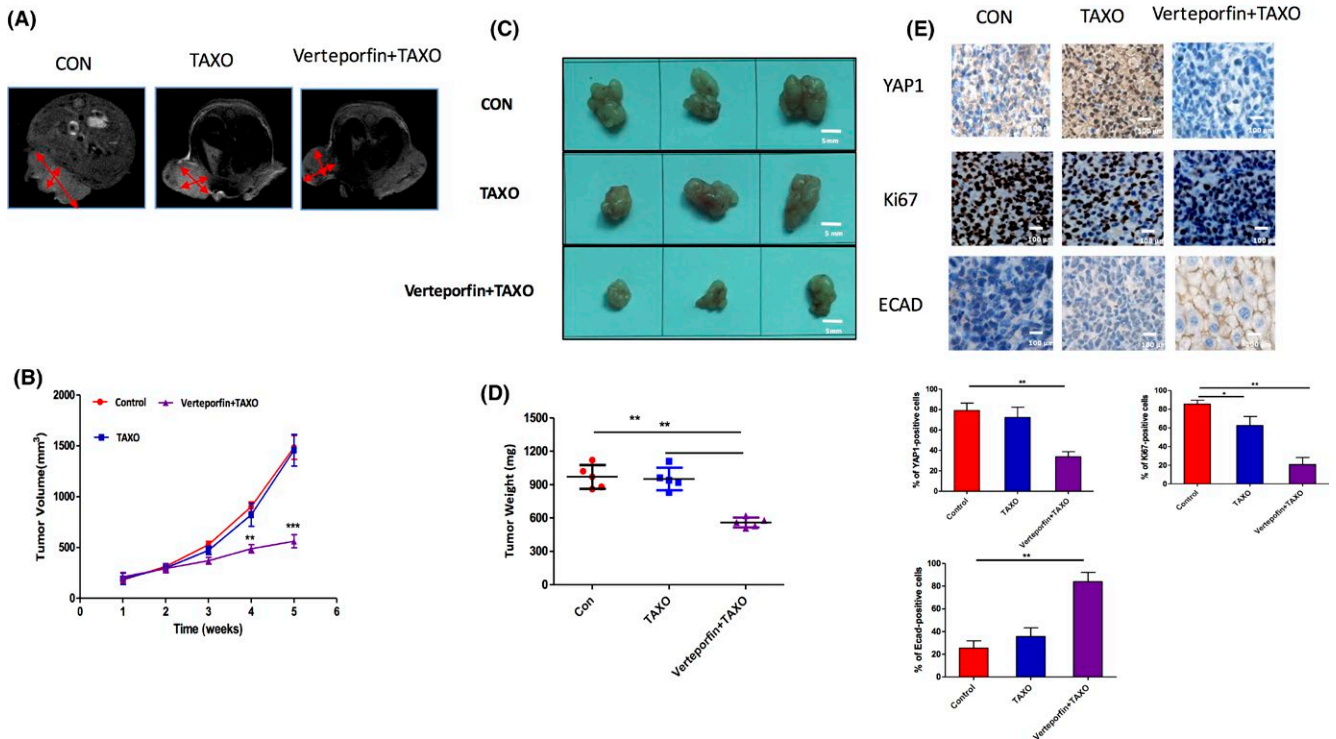


FIGURE 5 Verteporfin reverses taxol resistance of triple-negative breast cancer (TNBC) in vivo. A, B, Tumor volume was measured using magnetic resonance imaging in a 231-taxol resistant (231R) xenograft model. C, Representative images of xenograft tumor are seen. D, Tumor weight was measured in plots. E, Yes-associated protein 1 (YAP1), Ki67 and E-cadherin expression were detected by immunohistochemistry in control, 231-taxol resistance and verteporfin + 231-taxol resistance groups. Scale bars, 100 μm and 5 mm. Data are presented as mean and SEM from three independent experiments. * $P < .05$. ** $P < .01$. *** $P < .001$

study on verteporfin inhibition function in vivo. Mouse xenograft results showed that verteporfin significantly reduced the volume of taxol-resistant tumors in mice (Figure 5A-D). Additionally, we observed that verteporfin decreased Ki67 expression and increased E-cadherin staining when YAP1 protein was knocked down (Figure 5E). Decrease in tumor size, decreased Ki67 and increased E-cadherin staining were also observed in shYAP1 231 R cells xenograft models (Figure S4A-C). In addition, the overexpressed YAP1 protein in 231 R cells partially reversed xenograft tumors sensitive to taxol treatment (Figure S4A,D,E). Thus, verteporfin reverses taxol treatment resistance of TNBC tumor in vivo.

4 | DISCUSSION

Yes-associated protein 1 has been studied regarding its function as an oncogene in the promotion of neoplastic transformation such as in hepatocellular carcinoma, colon adenocarcinoma and ovarian carcinoma and others.¹¹⁻¹³ Because YAP1 function has been linked to neoadjuvant chemotherapy resistance, several drugs have been used to block the activation of YAP1.^{14,15} Verteporfin is a cyclic benzoporphyrin derivative that interrupts YAP/TAZ interaction and thereby inhibits YAP-interacting gene pathways.¹⁵ Other clinical trials tested verteporfin in combination drugs in the setting of pancreatic carcinoma and were proven to be effective.¹⁶ In our study, we generated

a TNBC taxol-resistant cell line to investigate anti-YAP1 expression in the reverse of TNBC chemoresistance.

We showed that YAP1 overexpression was associated with early relapse of TNBC patients with taxol chemoresistance. In the in vitro experiments, we showed that knockdown of YAP1 by verteporfin has significant effects on the inhibition of cell migration and enhanced apoptosis and autophagy in MDA-MB-231 taxol resistance. Inhibition of YAP1 with verteporfin also interrupted Bcl2 and BAX expression and reversed TNBC taxol resistance through the EMT pathway. Finally, verteporfin showed its ability in reverse taxol chemoresistance in TNBC mice xenographic tumor growth.

In clinical studies, therapy with adjuvant cisplatin or platinum-based agents in TNBC patients has not reached complete pathological remission.^{17,18} Other studies indicate that triple-negative cancers showed insensitivity to taxol-based treatment, which may be due to BRCA1 mutations or TP53 gene mutations.^{19,20} Our study showed that YAP1 overexpression was associated with early relapse of TNBC patients. In addition, we showed that verteporfin, a YAP1 small molecular inhibitor, could serve as a sensitizer in taxol-based chemotherapy in triple-negative cancer in vitro and in vivo. We hypothesize that verteporfin can be considered a potential tailored therapy for TNBC patients in the future. Our results also suggest that YAP1 could be seen as a biomarker for the prognosis of TNBC patients.

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CONFLICTS OF INTEREST

Authors declare no conflicts of interest for this article.

ORCID

Xi Wei  <https://orcid.org/0000-0003-4734-3900>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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