# Telmisartan prevents proliferation and promotes apoptosis of human ovarian cancer cells through upregulating PPARγ and downregulating MMP-9 expression

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**Abstract.** The mortality rate of ovarian cancer is the highest of all gynecological malignances. Telmisartan is a commonly used clinical angiotensin receptor blocker, which has anti-hypertensive, anti-inflammatory and antithrombotic effects. In the present study, it was investigated whether telmisartan could exert anticancer effects on ovarian cancer cells through upregulating peroxisome proliferator-activated receptor γ (PPARγ) and downregulating matrix metalloproteinase-9 (MMP-9) expression. A 3.3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay was conducted to analyze the proliferation of HEY cells. A Caspase-3 Activity Assay kit and an Annexin V-fluorescein isothiocyanate/propidium iodide kit were used to analyze the apoptosis of HEY cells. In addition, a gelatin zymography assay and reverse trancription-quantitative polymerase chain reaction were included to analyze the expression of PPARγ and MMP-9 in HEY cells. The data showed that telmisartan could significantly decrease cell viability and induce the apoptosis of HEY cells in a time- and dose-dependent manner. Furthermore, telmisartan could also dose-dependently increase the expression of PPARγ and decrease the expression of MMP-9 in HEY cells. In addition, downregulation of the expression of PPARγ by small interfering (si)RNA could reduce the effect of telmisartan on ovarian cancer cells and increase the expression of MMP-9. In conclusion, the results indicated that telmisartan prevents proliferation and promotes apoptosis of human ovarian cancer cells by upregulating PPARγ and downregulating MMP-9 expression.

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## Introduction

Ovarian cancer is one of the most common types of malignant tumor of the female reproductive organs, with the third highest incidence rate after cervical cancer and uterine cancer (1). The mortality rate of epithelial ovarian cancer is the highest of all gynecological tumors (2). Among the different types of ovarian cancer, epithelial tumors are the most common, and the second most common are malignant germ cell tumors (3). Patients with epithelial ovarian cancer with tumors that are confined to the ovaries at the time of surgery only account for 30% of all cases, with the majority experiencing spread to the uterus, bilateral accessory, and omental and pelvic organs; therefore, there is a problem with early diagnosis (4).

Peroxisome proliferator-activated receptor (PPAR) is a type of nuclear transcription factor activated by ligands, and is a member of the nuclear hormone receptor superfamily. Recent research has demonstrated that PPARγ is highly expressed in a number of types of cancer, including stomach, pancreatic, breast, esophageal and lung cancer (5-9). Certain studies have indicated that PPARγ can adjust the level of matrix metallo-proteinases (MMPs) and affect trophoblast invasion, resulting in the restriction of fetal growth (10-12). Thus, agonists of PPARγ can effect the activity of MMP-9 (13). A previous study showed that following ligand activation in K562 and HL-60 human myeloid cell leukemia cell lines, PPARγ can inhibit the adhesion and invasion of cells by affecting the expression of MMP-2 and -9 (14).

Telmisartan is a common clinical antihypertensive agent which is an angiotensin receptor inhibitor (15). Studies have demonstrated that telmisartan not only protects against cerebral ischemia through adjusting blood pressure, but also by activating PPARγ, which results in antioxidant and anti-inflammatory effects reducing the volume of cerebral infarction and protecting against cerebral ischemia (16-17). Telmisartan can inhibit MMP-9 by activating PPARγ, which significantly reduces ventricular remodeling after myocardial infarction and retards atherosclerosis (18). Therefore, the present study was conducted to investigate the anticancer effects of telmisartan.

In the current study, telmisartan was demonstrated to decrease proliferation and promote the apoptosis of human ovarian cancer cells by upregulating PPARγ and downregulating MMP-9 expression.

## Materials and methods

*Chemicals*. Dulbecco's modified Eagle's Medium (DMEM) and fetal bovine serum (FBS) were purchased from Gibco-BRL (Rockville, MD, USA). 3.3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) was purchased from Promega Corporation (Madison, WI, USA). The Caspase-3 Activity Assay kit was purchased from Beyotime Institute of Biotechnology (Nanjing, China). The Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) kit was purchased from BD Pharmingen (San Diego, CA, USA). RNeasy Plus Mini kit was purchased from Nanjing KeyGen Biotech Co., Ltd. (Nanjing, China). Transcriptor First Strand cDNA Synthesis kit was purchased from Sangon Biotech (Shanghai, China).

*Cell culture*. HEY human ovarian cancer cells were obtained from the Animal Lab of the First Affiliated Hospital of Dalian Medical University (Dalian, China). HEY cells were maintained in DMEM, containing 10% FBS, 100 U/ml penicillin and 100 mg/ml streptomycin (Amresco LLC, Solon, OH, USA) at 37°C in 5% $CO_2$.

*MTT assay*. HEY cells ($1 \times 10^4$) were seeded in 96-well plates and treated with telmisartan (Sigma-Aldrich, St. Louis, MO, USA) (Fig. 1) at different concentrations (0, 1, 10 and 100 μM) for 0, 24, 48 and 72 h (19). The proliferation of HEY cells was determined by an MTT assay. MTT (20 μl, 5 mg/ml) was added to each well and incubated for 4 h. Then, the medium in each well was removed. Approximately 150 μl dimethylsulfoxide (Amresco LLC) was added to each well and incubated for 10 min at room temperature whilst being agitated. The plates were read with a microplate reader (Model 680; Bio-Rad Laboratories, Inc., Hercules, CA, USA) at 570 nm.

*Caspase-3 activity measurement*. HEY cells ($2.0 \times 10^5$/ml) were plated in 6-well plates and incubated for 24 h. After treatment with telmisartan (0, 1, 10 or 100 μM), the activity of caspase-3 was detected using the caspase-3 colorimetric assay kit (Beyotime Institute of Biotechnology), according to the manufacturer's instructions. Samples were measured with an ELISA reader (Model 680; Bio-Rad Laboratories, Inc.) at a wavelength of 405 nm.

*Flow cytometric analysis for detecting cellular apoptosis*. In accordance with the manufacturer's instructions, apoptosis was detected using an Annexin V-FITC/PI kit. Briefly, HEY cells were stained with 5 μl Annexin V-FITC and 5 μl PI for 15 min at room temperature in the dark. Cell apoptosis was determined using a flow cytometer (Gallios; Beckman Coulter, Inc., Brea, CA, USA).

*Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis of PPARγ expression*. In accordance with the manufacturer's instructions of the RNeasy Plus Mini kit,
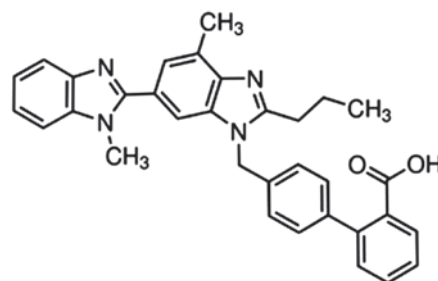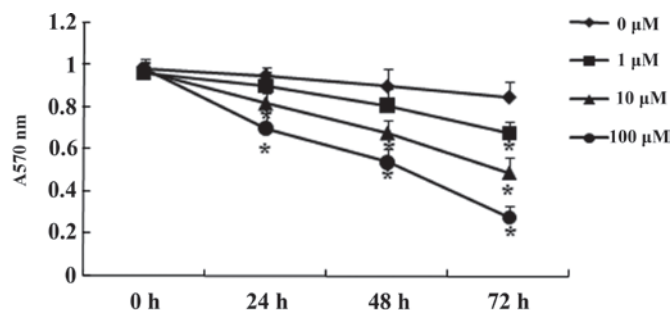


Figure 1. Chemical structure of telmisartan.



Figure 2. 3.3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide analysis of cell proliferation following treatment with different concentrations of telmisartan (0, 1, 10 and 100 μM). *P<0.01 compared with the 0 μM telmisartan treatment group.

total RNA (1 μg) was isolated from HEY cells. cDNA was produced by reverse transcription using the Transcriptor First Strand cDNA Synthesis kit. The synthesized cDNA was used as a template to estimate the quantity of gene transcription by qPCR. The amplification conditions were as follows: 94°C for 10 sec, 58°C for 30 sec, and 72°C for 10 sec for 35 cycles. The following primer sequences were used: PPARγ, forward, 5'-GCGGAAGCCCTTTGGTGA-3' and reverse 5'-TGCAGC AGGTTGTCTTGGATG-3'; GAPDH, forward, 5'-CCCCCA ATGTATCCGTTGTG-3' and reverse 5'-TGCAGCAGGTTG TCTTGGATG-3'. The Ct was obtained using the Sequence Detection System software (Applied Biosystems; Thermo Fisher Scientific, Waltham, MA, USA).

*Analysis of MMP-9 expression*. A gelatin zymography assay was performed to analyze the expression of MMP-9. Briefly, the medium of each well was collected, combined with an equal volume of sodium dodecyl sulfate (SDS) sample buffer and resolved in 10% polyacrylamide gels containing 0.1% gelatin (Beyotime Institute of Biotechnology). After electrophoresis, the gel was washed with 2.5% Triton X-100 (Beyotime Institute of Biotechnology) for 0.5-1 h, and incubated in a reaction buffer at 37°C for 12 h. Following incubation, the gel was stained with 0.05% Coomassie brilliant blue R-250 (Bio-Rad Laboratories, Inc.). A gelatin zymography assay was performed to analyze the expression of MMP-9 as previously described (20).

*Silencing of PPARγ*. PPARγ small interfering (si)RNA was obtained from Sangon Biotech. The following primers were used: S1 forward primer: 5'-AGAUAAAGCUUCUGGAUU UdTdT-3' and reverse primer: 5'-dTdTUCUAUUUCGAAGAC CUAAA-3'; S2 forward primer: 5'-AGGAAAGACAACAGA
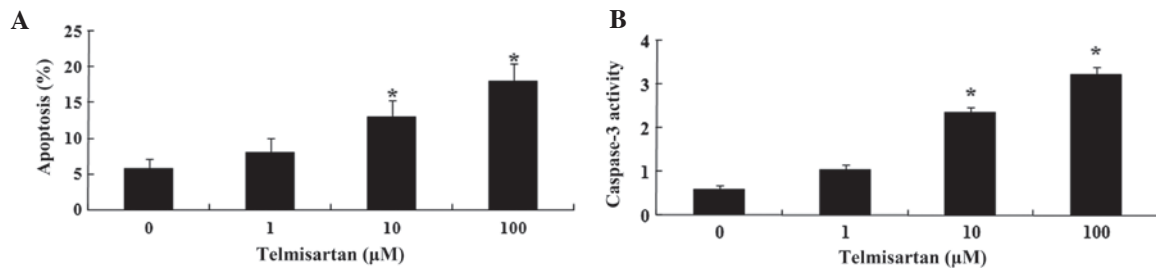
Figure 3. Flow cytometric analysis for detecting cellular apoptosis. (A) Telmisartan treatment dose-dependently promotes apoptosis as determined using flow cytometry. (B) The activity of caspase-3 in HEY cells. $^*$P<0.01 compared with the 0 $\mu$M telmisartan treatment group.
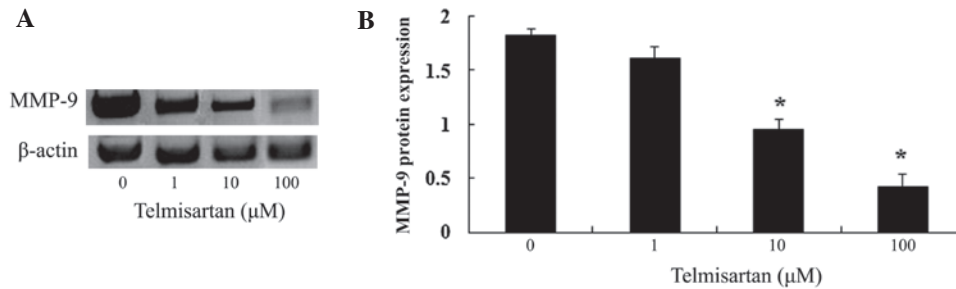


Figure 4. Effect of telmisartan on MMP-9 expression. (A) MMP-9 activity was dose-dependently reduced in HEY cells following treatment with telmisartan for 48 h as analyzed using gelatin zymography assays. (B) Quantitation of the results of the gelatin zymography assays. $^*$P<0.01 compared with the 0 $\mu$M telmisartan treatment group. MMP, matrix metalloproteinase.
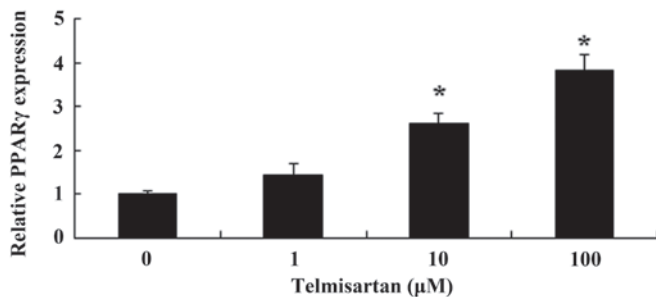


Figure 5. PPARγ expression following treatment with different concentrations of telmisartan (0, 1, 10 and 100 $\mu$M) for 48 h. $^*$P<0.01 compared with the 0 $\mu$M telmisartan treatment group.

CAAAdTdT-3' and reverse primer: 5'-dTdTUCCUUUCU GUUGUCUGUUU-3'; and S3 forward primer: 5'-GUACCA AAGUGCAAUCAAAdTdT-3' and reverse primer: 5'-dTdTCA UGGUUUCACGUUAGUUU-3'. PPARγ siRNA (100 mmol/l) was transfected into HEY cells using Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific.

*Statistical analysis.* Data were analyzed using SPSS 13.0 (Chicago, IL, USA). Values are expressed as the mean ± standard deviation of independent experiments. Differences were analyzed using analysis of variance or Student's paired t-test. P<0.05 was considered to indicate a statistically significant difference.

## Results

*MTT analysis of cell proliferation.* To evaluate the effect of telmisartan on HEY cells, cell proliferation was measured using an MTT assay. The cells were treated with telmisartan (0, 1, 10 and 100 $\mu$M) for 0, 24, 48 and 72 h, which resulted in significantly inhibited growth of HEY cells in a time- and dose-dependent manner (Fig. 2).

*Flow cytometric analysis for detecting cellular apoptosis.* As telmisartan significantly inhibited the growth of HEY cells, it was further explored whether telmisartan may have an effect on apoptosis. Flow cytometric analysis showed that telmisartan treatment for 48 h resulted in concentration-dependent apoptosis of HEY cells (Fig. 3A). Following treatment with telmisartan (10 and 100 $\mu$M) for 48 h, the level of apoptosis was significantly increased. In addition, the activity of caspase-3 in HEY cells was significantly increased (Fig. 3B).

*Effect of telmisartan on MMP-9 expression.* Following treatment (48 h) with telmisartan (0, 1, 10 and 100 $\mu$M), the expression of MMP-9 protein in HEY cells was analyzed using gelatin zymography assays (Fig. 4A). Treatment with telmisartan at concentrations of 10 and 100 $\mu$M significantly decreased the expression of MMP-9 protein (Fig. 4B).

*Telmisartan activates PPARγ expression.* Quantitative analysis of PPARγ expression in HEY cells showed that treatment with telmisartan (10 and 100 $\mu$M) for 48 h could significantly increase the expression of PPARγ (Fig. 5).

*PPARγ siRNA can reverse the effects of telmisartan.* PPARγ siRNA was transfected into HEY cells. The results indicated that transfection of PPARγ siRNA significantly reduced the expression of PPARγ in HEY cells (Fig. 6A). Notably, it was observed that downregulating the expression of PPARγ could prevent the effects of telmisartan on cell proliferation (Fig. 6B)
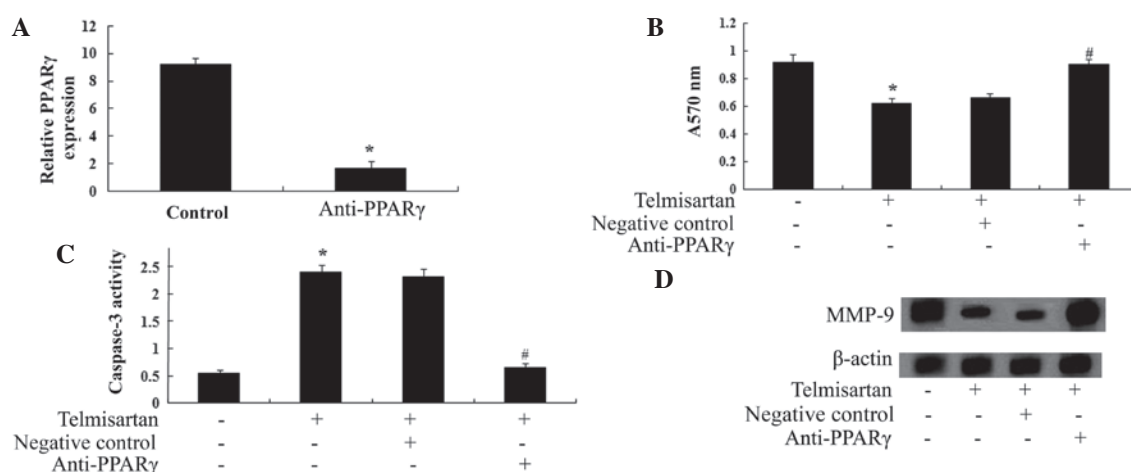
Figure 6. PPARγ siRNA can reverse the effect of telmisartan. (A) PPARγ siRNA decreased the expression of PPARγ in HEY cells. Following treatment with telmisartan (10 $\mu$M) for 48 h, PPARγ siRNA significantly (B) promoted cell proliferation, (C) inhibited cell apoptosis of HEY cells; and (D) increased MMP-9 expression in HEY cells. *P<0.01 compared with the 0 $\mu$M telmisartan treatment group and #P<0.01 compared with the telmisartan-treated group transfected with negative control.

and the activity of caspase-3 (Fig. 6C). It also increased the expression of MMP-9 protein in HEY cells (Fig. 6D) at 48 h.

## Discussion

At present, the mortality rate of ovarian cancer is the highest of all gynecological malignant tumors. Its treatment utilizes the combination of surgery and chemotherapy (21). In the chemotherapy of ovarian cancer, platinum drugs, such as cisplatinum, are important, while the emergence of drug resistance to cisplatinum in ovarian cancer restricts the clinical efficacy (22). Thus, enhancing the sensitivity to chemotherapeutic drugs is key in the treatment of ovarian cancer and is a focus of research. Overall, in the present study it was demonstrated that treatment with telmisartan significantly inhibited the growth of HEY cells in a time- and dose-dependent manner. In addition, telmisartan could also induce apoptosis of HEY cells and decrease the activity of caspase-3 in HEY cells. In a previous study, it was determined that telmisartan increased the apoptosis of human renal cell carcinoma cells via downregulation of Bcl-2 and involvement of caspase-3 (23). In addition, telmisartan has been previously demonstrated to significantly inhibit growth of human endometrial cancer cells (24).

Through the adjustment of the expression of the relevant genes, PPARγ is important in regulating fat formation, lipid metabolism, energy metabolism and the immune system. In addition, it is associated with the generation and development of numerous diseases, such as diabetes, obesity, metabolic syndrome and hypertension (25). PPARγ is predominantly expressed on the surface of granule cells of follicles during the growth period in ovarian tissue, however, there is only low expression in theca and luteal cells (26). PPARγ participates in the regulation of normal physiology of the ovary, luteinizing hormone peak reduction and the secretion of estrogen and progesterone, which can affect the growth of follicles, ovulation and the quality of ovum (21). In the present study, treatment with telmisartan could significantly increase the expression of PPARγ. In addition, a previous study has shown that telmisartan activates PPARγ and does not affect osteoblast

differentiation or bone mass (27). Telmisartan can also protect the nutrient deprivation-induced apoptosis of cerebellar granule cells *in vitro* through activation of the PPARγ pathway (28).

Studies have also demonstrated that in the renal cortex or fiber cells, PPARγ agonists can improve renal tubulointerstitial fibrosis process by preventing cell growth and adjusting the levels of MMP-9, TIMP-1 and TIMP-2 (29,30). In early pregnancy chorionic villi, the expression of PPARγ is negatively correlated with the levels of MMP-2 and MMP-9, which suggests that PPARγ regulates the expression of MMP-2 and MMP-9, affecting the invasion of trophoblast cells (31). The results of the present study showed that treatment with telmisartan could significantly decrease the expression of MMP-9 protein. Araújo *et al* (32) reported that telmisartan can reduce COX-2, MMP-2, MMP-9 and RANKL/RANK in ligature-induced periodontitis in rats. Telmisartan can weaken acute myocardial infarction through downregulation of MMP-2 and MMP-9 (33). These results suggest that downregulating the expression of PPARγ could restrain the effect of telmisartan on anti-proliferative and apoptotic effects, and up-regulation the expression of MMP-9 protein level in HEY cells. Telmisartan is a novel and specific Ang II receptor antagonist with long term efficiency, which not only effectively decreases blood pressure, but also has anti-inflammatory, anti-thrombotic and other non-antihypertensive effects (30,34). Telmisartan has antihypertensive effects and can affect the expression of PPARγ in muscle. Overall, in addition to inhibiting cell growth by reducing proliferation and inducing apoptosis, telmisartan may have therapeutic potential in ovarian cancer by upregulating PPARγ and downregulating the MMP-9 expression signaling pathway. Further studies are required to clarify additional mechanisms underlying the effects of telmisartan on ovarian cancer cells.

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