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*Original Research Article*

# Curcumin Promotes Mitochondrial Apoptosis of Cancer-derived Lung Cancer Stem Cells and Cisplatin Sensitization Through BH3-only Dephosphorylation

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**Zhigang Lu[1], Chunlin Li[1] and Jiayang Sun[1]**

## Abstract

**Background:** Lung cancer's mortality ranks first among other cancers. Several studies have shown the role of microRNAs in the pathogenesis of lung cancer.
**Objectives:** This study investigates microRNA-1297's (miR-1297) role in lung cancer.
**Materials and Methods:** Cisplatin (DDP)-resistant cells A549/DDP and NCI-H460/DDP were utilized to measure cell proliferation and BH3-only expression.
**Results:** miR-1297 was upregulated in A549/DDP and NCI-H460/DDP cells, and BH3-only was downregulated. DDP inhibited the proliferation of A549/DDP and NCI-H460/DDP cells. BH3-only is the target gene of miR-1297. BH3-only was upregulated by the miR-1297 inhibitor, resulting in increased cell apoptosis, impaired proliferation, and drug resistance.
**Conclusion:** DDP resistance in lung cancer is associated with the miR-1297 level. Its downregulation induces DDP drug resistance by upregulating BH3-only.

## Keywords

Lung cancer, drug resistance, microRNA-1297, BH3-only

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## Introduction

Lung cancer's mortality ranks first among other cancers (Siegel et al., 2023), with an increased incidence in China (Jenkins et al., 2023). Although progress has been made, small cell lung cancer treatment has not changed too much (Bogart et al., 2023; Feng et al., 2023; Zheng et al., 2023). At present, the main treatment of lung cancer is multidisciplinary comprehensive treatment (Shreves et al., 2023).

Even for surgically resected patients, except for stage IA, chemotherapy has certain value (Lin et al., 2021). Several clinical trials have confirmed the efficacy of chemotherapy. However, affected by various factors such as curative effect and treatment cost, it is still challenging to determine the standard regimen at present (Felip et al., 2010; Rossi et al., 2012; Simeone et al., 2019). Curcumin is an active ingredient extracted from the rhizomes of turmeric and tulip and is a natural medicine with low toxicity and high safety (Novello et al., 2022). Curcumin has a certain inhibitory effect on lung cancer growth, proliferation, and invasion, but its role in stem cells is unclear.

Cisplatin (DDP) is a chemotherapy drug used to treat non-small cell lung cancer (NSCLC). It has been used since the 1970s and is considered a foundation treatment for advanced NSCLC (Rotolo et al., 2014). Chemoresistance, however, limits the application in the clinic (Fennell et al., 2016). Therefore, it is necessary and urgent to find a drug that can sensitize DDP for combined treatment.

Our research focuses on the DDP-sensitizing mechanism of curcumin on lung cancer stem cells through BH3-only dephosphorylation and provides help for improving the efficacy of treating lung cancer. The schematic diagram of the mechanism is shown in Figure 1.

## Materials and Methods

### *Instruments and Reagents*

Curcumin (Sigma, USA), DDP for injection (Qilu Pharmaceutical Co. Ltd., Zhunzi H20023461), MTT kit

[1]Department of Thoracic Surgery, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, China

**Corresponding author:**
Jiayang Sun, Department of Thoracic Surgery, Affiliated Hospital of Inner Mongolia Medical University, No. 1, North Passage Road, Huimin District, Hohhot, Inner Mongolia 010000, China.
E-mail: sunjia19yang@163.com

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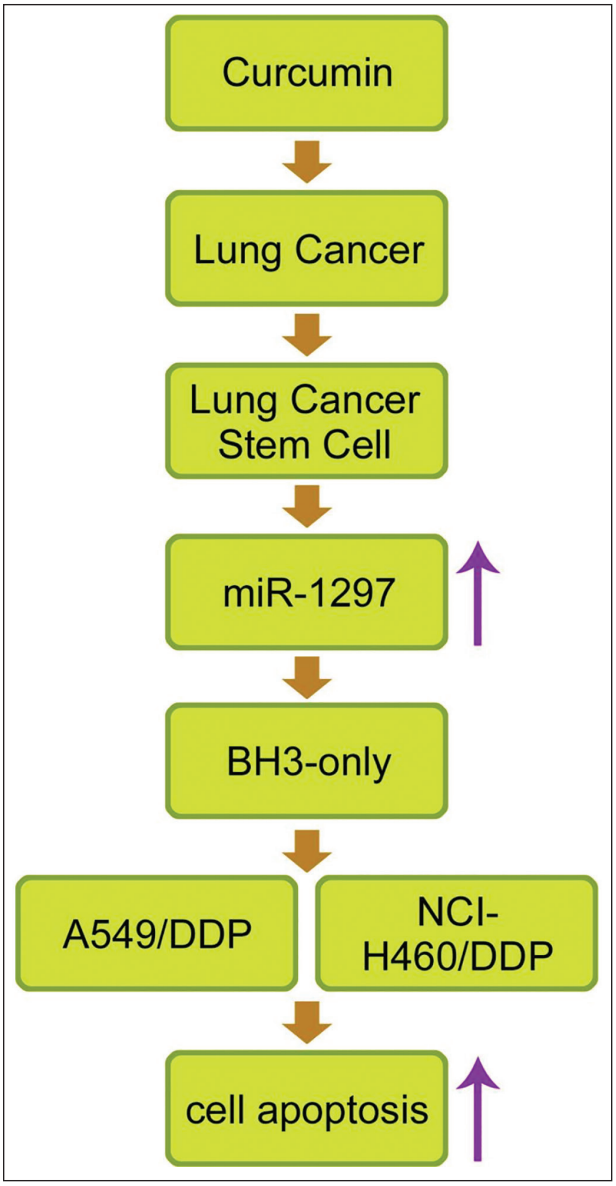



**Figure 1.** Schematic Diagram of the Mechanism.

(Tianjin Baihao Biotechnology Co. Ltd.), CD133 antibody, fetal bovine serum RPMI-1640, Transwell chamber reagent box, high power mirror, BCA kit, 5% skimmed milk powder, 0.4% crystal violet, 0.6 mg/mL oligomycin, TD-20/20 photometer (Turner Company, USA). The molecular formula is shown in Figure 2.

### *Experimental Cells*

Sorting and identification of stem cells: Collect A549 cells in a good growth state, count the cells, adjust the cell density, add CD133 antibody and blocking solution, and incubate in the dark for 30 min; wash; collect with a separation column. Negative binding cells and positive binding cells were cultured. The self-renewal ability test and the soft agar colony formation test identified the stemness of cultured cells. The results showed that the renewal ability of the second-generation cell spheres gradually increased with time, and the cell colony formation rate was 80.12%, which met the experimental needs.

### *Cell Proliferation Detection*

Cells were subpackaged and cultured in 96 culture plates, and after the cell lines adhered to the wall, the cells were jointly treated at a given concentration and time and centrifuged (2,200 × *g*) for 5 min to obtain supernatant, followed by the addition of dimethyl sulfoxide (DMSO) and measurement of optical density (OD) values at 490 nm.

### *Apoptosis Detection*

Cells were harvested from culture or tissue, washed, and resuspended. For experiments requiring specific cell population identification, cells were stained with fluorescently labeled antibodies or dyes. The flow cytometer (BD FACSCanto II) was calibrated using standard calibration beads to ensure accurate fluorescence and size measurements. Appropriate lasers and detectors were configured based on the fluorophores used in the experiment. A small aliquot of the cell suspension was

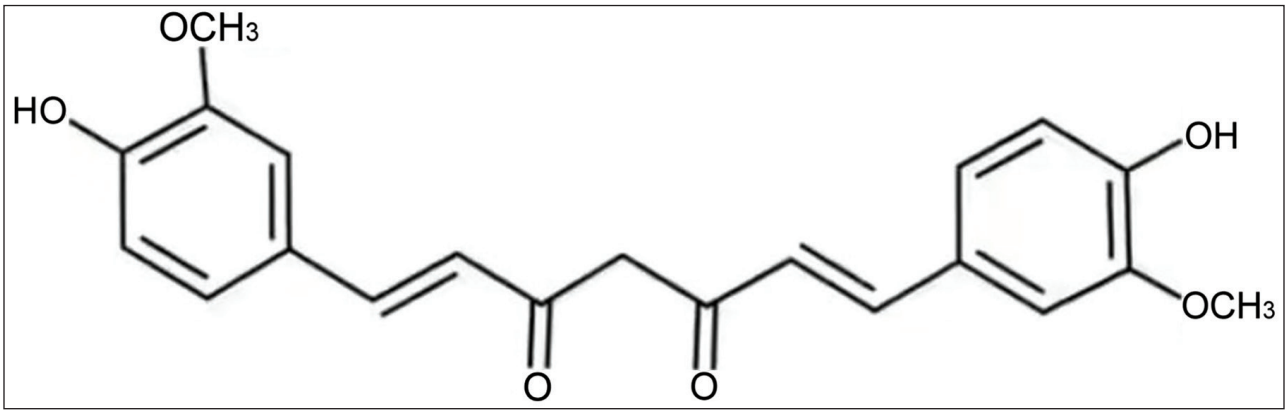



**Figure 2.** Molecular Formula of Curcumin.

run to optimize instrument settings, including voltage, gain, and threshold. Once optimized, the full sample was analyzed. Cells were passed through a laser beam, and scattered light (forward scatter, FSC; side scatter, SSC) and fluorescence signals were detected by photomultiplier tubes (PMTs). Data were collected using flow cytometry software (BD FACSDiva). To assess apoptosis, cells were stained with Annexin V-FITC/propidium iodide (PI) using a commercial kit (e.g., BioLegend) and analyzed by flow cytometry.

### *Detection of Mitochondrial Adenosine Triphosphate (ATP) Level*

ATP bioluminescence was used to detect mitochondrial ATP levels, the concentration of lung cancer stem cells was adjusted to 1 × $10^6$/mL, inoculated into six-well culture plates, transfected with corresponding plasmids and cultured for 48 h, and converted by the difference of ATP production before and after adding 0.6 mg/mL oligomycin mitochondrial ATP content (oligomycin has the effect of inhibiting mitochondrial ATP synthase). ATP content was detected by a TD-20/20 photometer (Turner, USA).

### *Reverse Transcription Polymerase Chain Reaction (RT-PCR)*

The TRIzol method was used to extract cellular RNA, which was utilized for real-time quantitative PCR analysis by using SYBR Green Master Mix, double-distilled water, primers, and the synthesized cDNA to determine the expression of target genes using the primers shown in Table 1 (primers were designed by using Primer Premier). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a control to normalize RNA input. Software analysis –ΔΔCT comparison method (Livak & Schmittgen, 2001).

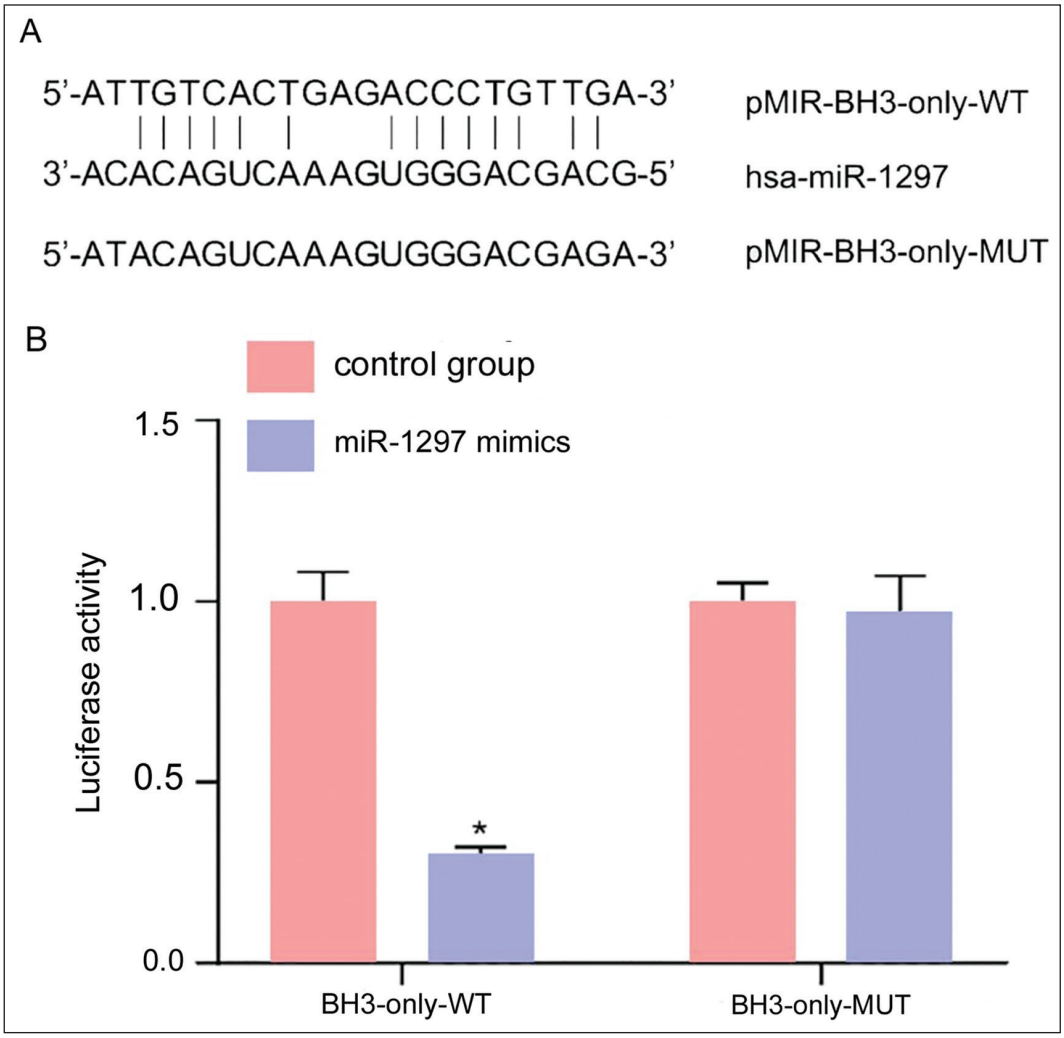



**Figure 3.** There is a Targeted Regulatory Relationship Between MicroRNA-1297 (miR-1297) and BH3-only mRNA. (A) Schematic Diagram of the Interaction Site Between miR-1297 and 3′-UTR of BH3-only mRNA; (B) Dual Luciferase Gene Reporter Experiment.

**Note:** * represents $p < .05$ compared with miR-NC.

### Statistical Method

SPSS 19.0 software processed data displayed as mean ± standard deviation and assessed by one-way analysis of variance (ANOVA). $p < .05$ means a difference.

## Results

### MicroRNA-1297 (miR-1297) Targets BH3-only

miR-1297 could target BH3-only, as shown in Figure 3A, but the relative luciferase activity of miR-1297 mimic in cells transfected with pMIR-BH3-only-MUT was not changed (Figure 3B), indicating that miR-1297 could target BH3-only.

### Effect of Curcumin on DDP Sensitization

As shown in Figure 4A, CCK-8 test results show that under the same dose of DDP treatment conditions, proliferation activity of parental A549 (Figure 4B) and NCI-H460 cells (Figure 4B) was significantly lower than that in A549/DDP and NCI-H460/DDP cells. We selected the most suitable concentration of curcumin based on the $IC_{50}$ value. The $IC_{50}$ was 2.15 ± 0.26 μg/mL for A549 cells, 31.23 ± 2.13 μg/mL for A549/DDP cells, and the drug resistance index was 14.53.

**Table 1.** Real-time Polymerase Chain Reaction (PCR) Primers and Primer Sequences.

| Primer | | Sequence |
|---|---|---|
| BH3-only | Forward primer | 5′-GTTCCAGCCTCGGTTTCTA-3′ |
| | Reverse primer | 5′-TAGAAACCGAGGCTGGAAC-3′ |
| miR-1297 | Forward primer | 5′-TCGGCAGGTTCAAGTAATT-3′ |
| | Reverse primer | 5′-TCTCCAAAGGAGGTTACCTGC-3′ |
| GAPDH | Forward primer | 5′-CTCAACTGGTGTCGTGGA-3′ |
| | Reverse primer | 5′-AGTGATGGCATGGACTGTGG-3′ |

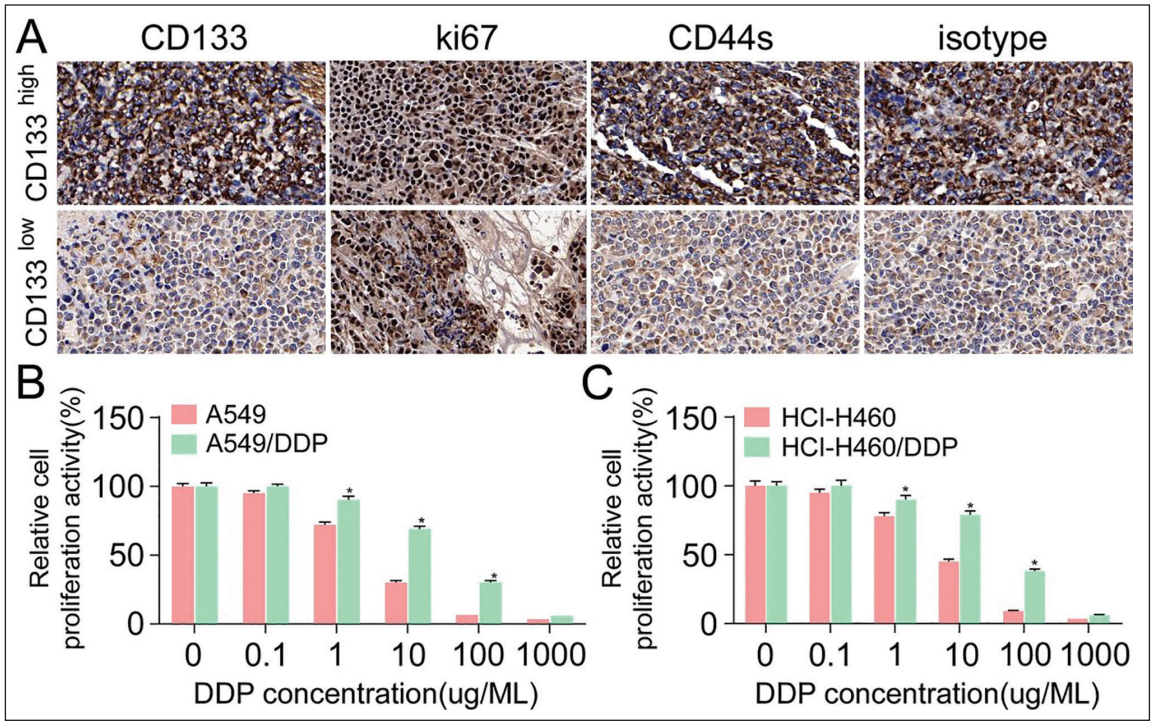



**Figure 4.** Effect of Curcumin on the Sensitization of Cisplatin. (A) The Expression of CD133 and CD44s Detected by Immunohistochemistry; (B) The Proliferation Activity of A549 and A549/DDP Cells was Detected by CCK-8 Assay; (C) The Proliferation Activity of NCI-H460 and NCI-H460/DDP Cells was Detected by CCK-8 Assay.

**Note:** * represents the comparison between the two groups, $p < .05$.

The $IC_{50}$ of NCI-H460 cells was 3.53 ± 0.29 μg/mL with a resistance index of 15.29 (Figure 4C).

### *Increased miR-1297 and BH3-only in Drug-resistant Lung Cancer Cells*

miR-1297 in lung cancer cells was significantly upregulated (Figure 5A). However, BH3-only mRNA was significantly downregulated (Figure 5B). Consistently, the BH3-only protein in lung cancer cells and drug-resistant cells was significantly reduced (Figure 5C).

### *miR-1297 Downregulation Reduces DDP Resistance and Increases Mitochondrial Apoptosis*

miR-1297 inhibitor significantly upregulated BH3-only in DDP-resistant cells (Figure 6A). miR-372 inhibitor also increased the expression of the BH3-only protein (Figure 6B). miR-1297 inhibitor could significantly increase apoptosis of A549/DDP and NCI-H460/DDP cells (Figure 6C), while the cell proliferation ability was significantly reduced (Figure 6D).

## Discussion

Due to differences in race, living habits, dietary structure, and others, the incidence of lung cancer in different countries and regions varies greatly. Nearly half of the world's lung cancer cases occur in China (Guo et al., 2018, 2022). In China, the number of new lung cancer patients is as high as 820,000 every year, and the proportion of new lung cancer deaths is 620,000 (Pirker, 2020). The pathogenesis of lung cancer is relatively hidden, and it does not cause obvious clinical symptoms in the early stage (Alanni et al., 2019). However, middle-advanced disease progresses rapidly, is characterized

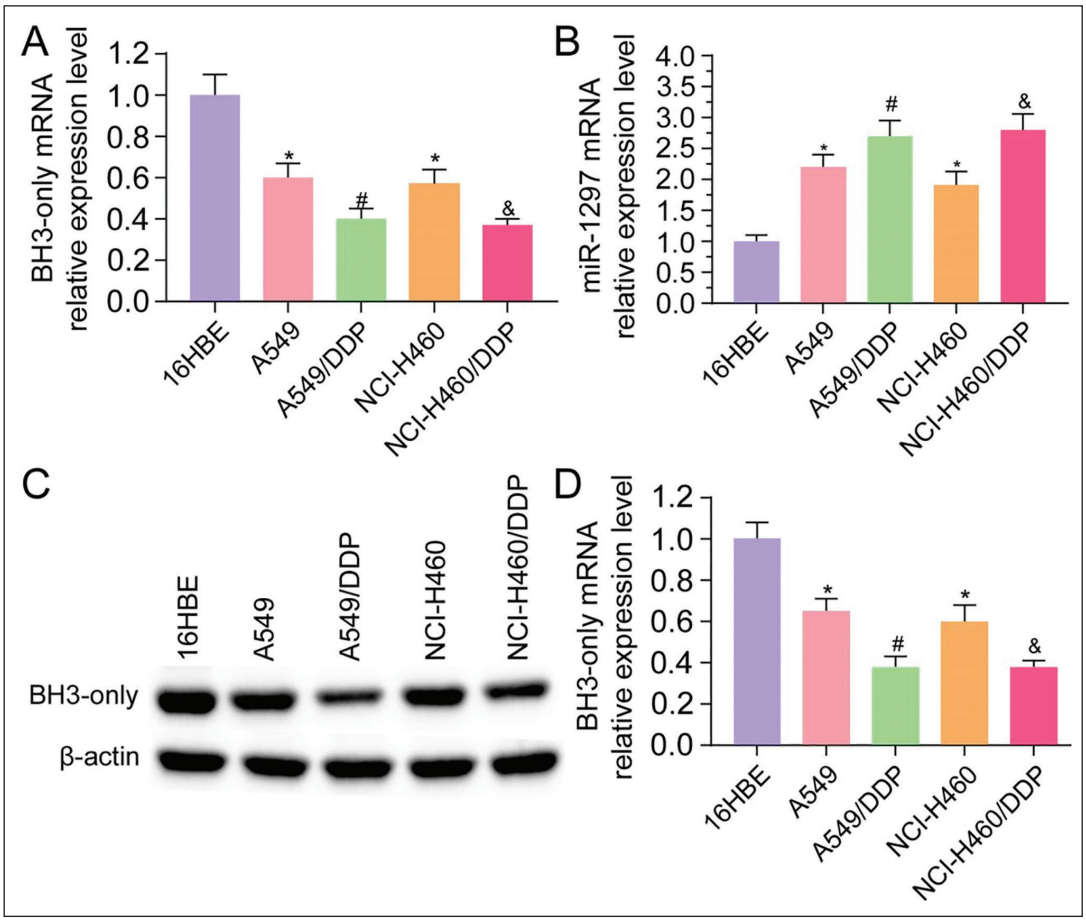



**Figure 5.** The Expression of MicroRNA-1297 (miR-1297) and BH3-only in Lung Cancer Drug-resistant Cells Increased. (A) Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) Detection of miR-375 Expression; (B) qRT-PCR Detection of BH3-only mRNA Expression; (C) Western Blot Detection of H3-only Protein Expression; (D) H3-only Protein in Cells of Each Group Statistical Comparison of Expression Levels.

**Note:** * represents $p < .05$ compared with 16HBE cells; # represents $p < .05$ compared with A549 cells; & represents $p < .05$ compared with NCI-H460 cells.

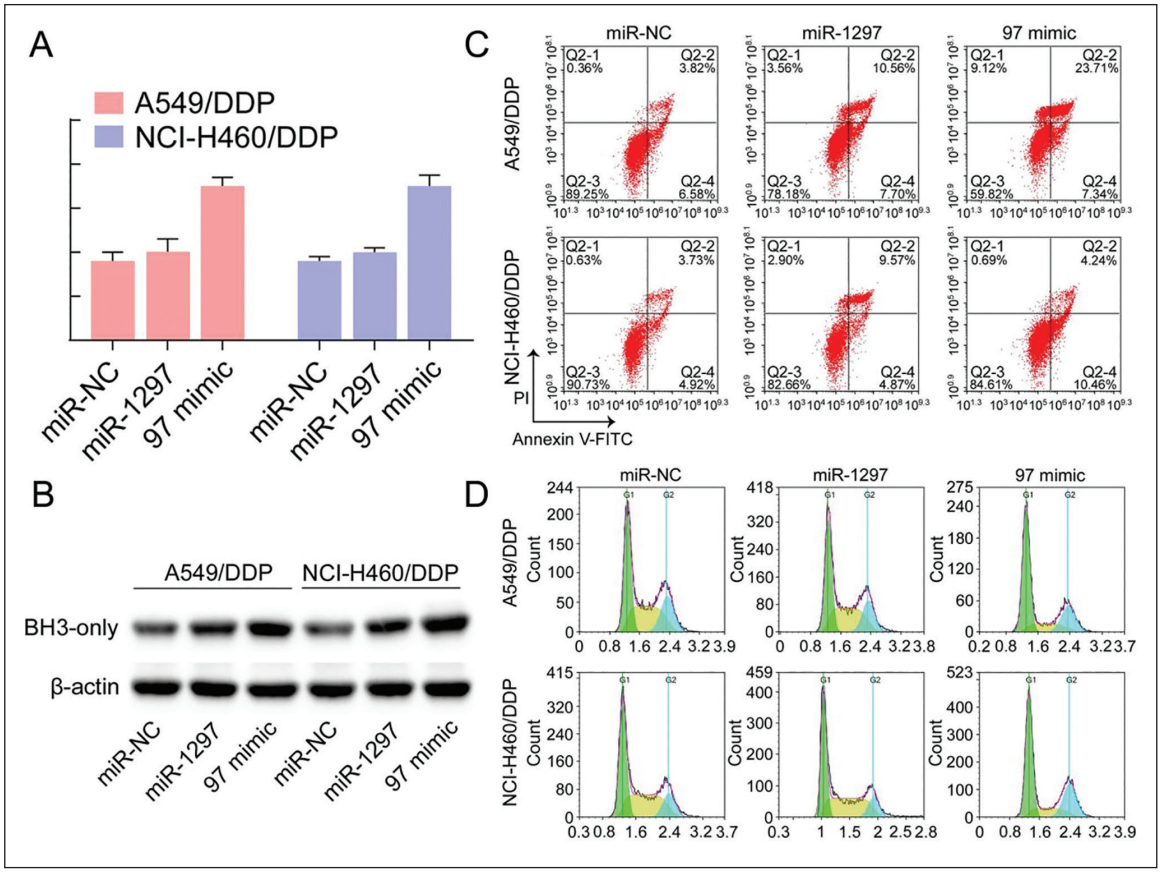



**Figure 6.** The Downregulation of MicroRNA-1297 (miR-1297) can Induce and Reduce the Cisplatin (DDP) Resistance of Lung Cancer Cells. Drug Properties Increase Mitochondrial Apoptosis. (A) Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) Detection of BH3-only mRNA Expression; (B) Western Blot Detection of BH3-only Protein Expression; (C) Flow Cytometry Detection of Cell Apoptosis; (D) Flow Cytometry Detection of Cell Proliferation.

**Note:** * stands for the same compared with the miR-NC group, $p < .05$.

by high malignancy, easy invasion and distant metastasis, and low sensitivity to radiotherapy and chemotherapy. Therefore, the curative effect is usually unsatisfactory, and the survival and prognosis are also poor (Stinchcombe, 2016). Although comprehensive treatment measures such as surgical resection, radiotherapy, chemotherapy, and gene and tumor immunotherapy have made great progress and can prolong patients' lives, the prognosis is still poor, and the 5-year survival rate after surgery is usually only 15%–20% (Guo et al., 2019).

BH3-only is currently the most studied transcription factor. BH3-only belongs to a conserved transcription factor family, located on chromosome 6 (6q21), encoding a protein molecule composed of 673 amino acids. The BH3-only protein has a characteristic structurally conserved forkhead DNA-binding domain, which consists of a winged helix domain consisting of three α-helices, three β-sheets, and two wing structures (Matsumoto et al., 2022). BH3-only participates in the activities of tumor cells (Canis et al., 2013; Liu et al., 2015). miR-1297 is a microRNA that has been studied more and is involved in several cancers (Liu et al., 2015). This study assessed miR-1297's role in the DDP resistance of lung cancer cells.

According to the detection results of the CCK-8 experiment, DDP treatment can significantly inhibit cell proliferation, but has less effect on drug-resistant cells based on the $IC_{50}$ of parental cells and drug-resistant cells to DDP. We successfully established drug-resistant lung cancer cells and found higher miR-1297 and lower BH3-only levels.

Further analysis showed that the transfection of miR-1297 inhibitor could significantly upregulate BH3-only in DDP-resistant cells and increase cell apoptosis. The regulatory effect of miR-1297 in lung cancer was achieved by targeting and inhibiting the target gene LATS2 (Li et al., 2020). There are also research results showing the role of miR-1297 as an oncogene in the biological regulation of lung cancer cells. miRNA inhibitor PA-1 can significantly inhibit miR-1297 levels and weaken the proliferation activity and clone formation ability of lung cancer AGS cells (Wang, Li et al., 2016). We found that the miR-1297 inhibitor inhibited lung cancer cell proliferation and induced apoptosis, which was reversed by miR-1297 mimics. 8-mer LNAs inhibit lung cancer cell behaviors by targeting and antagonizing the effect of miR-1297 and attenuate lung cancer cell growth in animals (Wang, Xu et al., 2016). Our

study revealed that the increased miR-1297 level can inhibit the expression of BH3-only, promote lung cancer cell proliferation, reduce apoptosis, and enhance DDP drug resistance function in sex. However, the exact mechanism is still unclear, and further research and testing are needed, which is also the limitation of this study.

## Conclusion

In conclusion, downregulating miR-1297 significantly reduces lung cancer drug resistance by increasing BH3-only protein levels and promoting cell proliferation, potentially through the regulation of apoptosis pathways. To validate this hypothesis, further investigation is required to elucidate the specific molecular mechanisms, including the direct targeting of BH3-only proteins (e.g., BIM, PUMA, or NOXA) by miR-1297, the activation of mitochondrial apoptosis pathways, and the potential involvement of other miR-1297-regulated targets related to cell cycles, DNA repair, or drug transport. Additionally, exploring the role of miR-1297 in modulating the tumor microenvironment, such as angiogenesis or immune evasion, may provide further insights into its impact on drug resistance. Establishing lung cancer animal models with low miR-1297 expression and developing targeted delivery systems for miR-1297 inhibition will be critical for translating these findings into therapeutic strategies. Furthermore, evaluating miR-1297 as a diagnostic or prognostic biomarker could enhance its clinical applicability in lung cancer management.

### Abbreviations

DDP: Cisplatin; miR-1297: microRNA-1297.

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### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical Approval

This study was approved by the Ethics Committee of Affiliated Hospital of Inner Mongolia Medical University.

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### Informed Consent

NA.

### ORCID iD

Sunjia Yang https://orcid.org/0009-0000-2800-8993

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