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# Research Article
# miR-193a-3p Overexpression Inhibits Proliferation and Enhances Paclitaxel Chemosensitivity in Human Non-Small-Cell Lung Cancer Cells

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## Abstract

**Background and Objective:** Non-Small-Cell Lung Cancer Cells (NSCLC) exposes the uppermost transience rates amongst several types of cancer and it is the most recurrent cancer in the globe. This study was purposed to show the potential therapeutic role of miR-193a-3p as a promising tumour suppressor in human A549 NSCLC in combination with paclitaxel. **Materials and Methods:** A549 cells were treated with miR-193a-3p mimics and paclitaxel, alone and in combination. The cytotoxic effects of microRNA-193a-3p and paclitaxel were determined using an MTT assay. Apoptosis was assessed by ELISA cell death assay. Gene expression analyses were determined by quantitative Reverse transcription-polymerase Chain Reaction (qRT-PCR). **Results:** Results showed that the combination therapy reduced cell viability with an increase in apoptosis. In addition, miR-193a-3p replacement increased the expression levels of caspase-3 and caspase-9 and decreased the expression levels of MMP-9, vimentin and ROCK in combination treatment compared to the mono treatments groups. **Conclusion:** The findings suggest that miR-193a-3p replacement combined with paclitaxel could be considered as a new potential therapeutic approach for the improvement of NSCLC treatment.

Key words: Non-small cell lung cancer, miRNA, drug resistance, miR-193a-3p, apoptosis, invasion, chemotherapy, cisplatin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Non-small Cell Lung Cancer (NSCLC), as the most prevalent type of human lung cancer, is estimated to be a common cause of cancer-related deaths worldwide[1]. Despite huge advances in designing novel and more effective therapeutic strategies for combating NSCLC, it has still a poor prognosis with an estimated less than 15% 5-year survival rate[2]. Current therapeutic options for NSCLC include surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapy. Carboplatin, cisplatin and paclitaxel (Taxol) are the most common chemotherapeutic agents used in the chemotherapy regime for patients suffering from NSCLC[3-5]. Paclitaxel, with high anti-cancer effects, is reported to be strongly effective in NSCLC patients when used alone or in combination with other therapeutic strategies[6,7]. Binding to β-subunit of tubulin, hence suppressing the microtubules formations and consequently inhibiting cell cycle progression and inducing apoptosis is the most accepted underlying mechanism for anti-tumour effects of paclitaxel in various human malignancies[8,9]. Regulating major proliferative signalling pathways such as Akt, the Mitogen-Activated Protein Kinase (MAPK) signalling pathways and interacting with a key component of apoptosis such as Bcl-2 and caspase-3 are other mechanisms, by affecting of whom, paclitaxel exerts anti-cancer impact on cancer cells[10-13]. However, similar to other human malignancies, the acquisition of multidrug resistance against conventional chemotherapeutic agents including paclitaxel is a critical barrier against the successful and complete removal of cancer cells in NSCLC[14]. The mechanisms of paclitaxel resistance in NSCLC is not still completely understood. An accumulating number of recent studies have focused on the pivotal roles of microRNAs (miRNAs) in the initiation/progression, as well as the development of drug resistance in NSCLC[15,16]. miRNAs are small non-coding RNAs with a broad range of biological functions through binding and suppressing the translation of mRNA molecules of specific target genes to proteins[17]. These tiny RNA molecules have also been demonstrated to be valuable as prognostic and therapeutic targets in numerous cancer types including NSCLC[18,19]. In addition to crucial roles in the cancer cells proliferation, apoptosis, angiogenesis and metastasis, some aberrant expressions of some miRNAs such as miR-181a, miR-107 and miR-630 are demonstrated to be associated with the development of drug resistance in NSCLC[20,21]. miR-193a-3p is a tumour suppressor miRNA and its downregulation was frequently reported in tumour tissue from NSCLC patients[22]. miR-193a-3p have a critical function in the chemoresistance of epithelial breast cancer[23], ovarian cancer[24], bladder cancer[25] and colorectal cancer[26]. However, the role of miR-193a-3p in developing chemoresistance against paclitaxel in NSCLC has not been described yet.

Therefore, the present study aimed to investigate the effects of miR-193a-3p over expression on the chemosensitivity of A549 NSCLC cells to paclitaxel.

## MATERIALS AND METHODS

**Study area:** The study was carried out at the Department of Thoracic Surgery, Wuhan No. 1 Hospital Lab, China from March, 2020-April, 2021.

**Cell culture:** A549 human NSCLC cell lines were provided from the Pasteur Institute Iran National Cell Bank (Tehran, Iran). RPMI-1640 medium (Gibco) supplemented with 10% fetal bovine serum (FBS, Gibco) and 1% streptomycin/penicillin solution was used as a culture medium for cultivating A549 cells. The cells were grown at 37°C providing 5% $CO_2$. By reaching 70% confluence, the cells were trypsinized and subcultured.

**miRNA transfection:** For miRNA transfection, $2\times10^5$ cells were seeded in 6-well plates. About 24 hrs later, cells were treated with miR-193a-3p mimics (5'-UCAUCUCGCCCGCAA AGACA-3') and FITC-conjugated controls, which were designed and provided by GenePharma Co. (Shanghai). Final concentrations of miR-193a-3p were 50 and 100 pmol. The efficacy of miRNA transfection and its upregulation in A549 cells were evaluated by quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR).

**Cell proliferation assay:** To assess the effects of paclitaxel treatment, alone or in combination with miR-193a-3p, on the cellular proliferation, as well as the efficacy of miR-193a-3p on the chemosensitization to paclitaxel, MTT assay was applied in A549 cells. For this purpose, cells were seeded in the 96-well plate and treated with various concentrations of paclitaxel (up to 4 μM), in combination with miR-193a-3p. About 24 hrs later, the cells medium were replaced by a fresh culture medium containing 2 mg $mL^{-1}$ MTT solution (Sigma Aldrich, Germany) and were incubated for another 4 hrs. Dimethyl Sulfoxide (DMSO) was added to each well to dissolve formazan crystals. In the end, the absorbance values of each well were measured at 570 nm wavelength using a microplate reader (Tecan, Switzerland).

**qRT-PCR analysis:** Cells were assigned into five groups including control, miR-193a-3p, CTRL-miR, paclitaxel and paclitaxel+miR-193a-3p groups. The total RNA of cells in all

Table 1: List of primer sequences

| Primers | Forward and reverse | Sequences |
|---|---|---|
| Caspase-3 | F | 5´-TGTCATCTCGCTCTGGTACG-3´ |
| | R | 5´-AAATGACCCCTTCATCACCA-3´ |
| Caspase-9 | F | 5´-GCAGGCTCTGGATCTCGGC-3´ |
| | R | 5´-GCTGCTTGCCTGTTAGTTCGC-3´ |
| MMP-9 | F | 5´-TTGACAGCGACAAGAAGTGG-3 |
| | R | 5´-GCCATTCACGTCGTCCTTAT-3´ |
| Vimentin | F | 5´-AATCGTGTGGGATGCTACCT-3´ |
| | R | 5´-CAGGCAAAGCAGGAGTCCA-3´ |
| ROCK | F | 5´-AATCGTGTGGGATGCTACCT-3´ |
| | R | 5´-AAAACCCTCAGTGTGTTGTGC-3´ |
| c-Myc | F | 5´-AGGCTCTCCTTGCAGCTGCT-3´ |
| | R | 5´-AAGTTCTCCTCCTCGTCGCA-3´ |
| GAPDH | F | 5´-CAAGATCATCAGCAATGCCT-3´ |
| | R | 5´-GCCATCACGCCACAGTTTCC-3´ |
| U6 | F | 5´-CTTCGGCAGCACATATACTAGG-3´ |
| | R | 5´-TCATCCTTGCGCAGGGG-3´ |
| Has-miR-193a | Target sequence | 5´-UCAUCUCGCCCGCAA AGACA-3´ |

groups were extracted using a Trizol RNA extraction kit (GeneAll, Korea). Then the quality and quantity of extracted RNAs were evaluated by measuring absorbance at A260/A280 using a NanoDrop spectrophotometer (Thermo Fisher Scientific Life Sciences). RNA molecules were subjected to complementary DNA (cDNA) synthesis by the miRCURY LNATM Universal cDNA Synthesis kit following manufacturers' protocol (Exiqon, Vedbaek, Denmark). Then, the expression levels of target genes including miR-193a-3p, caspase-3, caspase-9, MMP-9, ROCK and vimentin, were measured by qRT-PCR reaction via a Takara SYBR Premix Ex Taq II reagent and corresponding primers (Table 1) in CFX96 Touch Real-TimePCR (BioRrad). Internal controls for targets genes and target miRNA in this study were GAPDH and U6.

**Cell death assessment:** To investigate the effects of miR-193a-3p on the paclitaxel-induced apoptosis, A549 cells were treated with miR-193a-3p and paclitaxel, alone or in combination and a Cell Death Detection ELISA kit was used. A density of $1\times10^4$ cells per well was seeded in 96-well plates. Then, the cells were treated with paclitaxel, miR-193a-3p and their combination for 48 hrs. Cell death was evaluated using a commercial ELISA kit following the manufacturer's protocol.

**Statistical analysis:** SPSS software was used to perform statistical analysis. Results were presented as Mean±SD from at least 3 independent experiments. The significance of differences between groups was estimated by the ANOVA, a p-value of less than 0.05 was considered to be statistically significant.

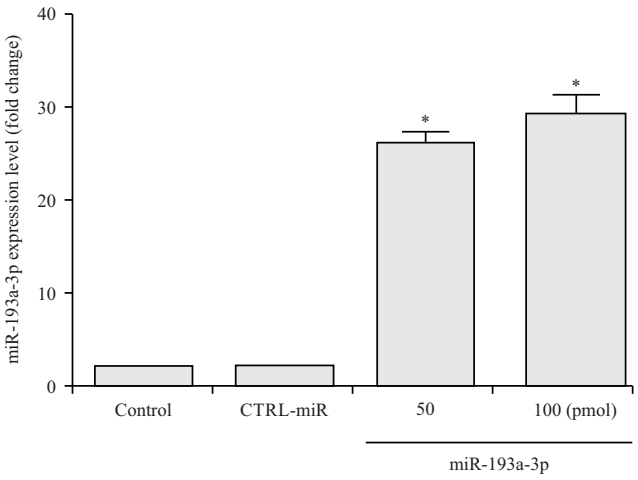


Fig. 1: miR-193a-3p expression levels 24 hrs after transfection
Quantitative reverse transcription-polymerase chain reaction results show upregulation of miR-193a-3p in a dose-dependent way after transfection compared to the negative controls. The data represent as Mean±standard deviation (triplicated), *p<0.05

## RESULTS

**miR-193a-3p was efficiently transfected into A549 cells:** Measuring the relative expression levels of miR-193a-3p in the A549 cells transfected by miR-193a-3p mimic was achieved by qRT-PCR to evaluate the efficacy of miR-193a-3p transfection. As shown in Fig. 1, after 24 hrs, the miR-193a-3p was significantly upregulated in a dose-dependent manner in A549 transfected cells in comparison to control cells ($p<0.05$), such that the expression levels of miR-193a-3p in cells transfected with 100 pmol mimics was significantly higher than cells transfected with 50 pmol miRNA mimic ($p<0.05$). In addition, CNTR-miR did not change the expression levels of

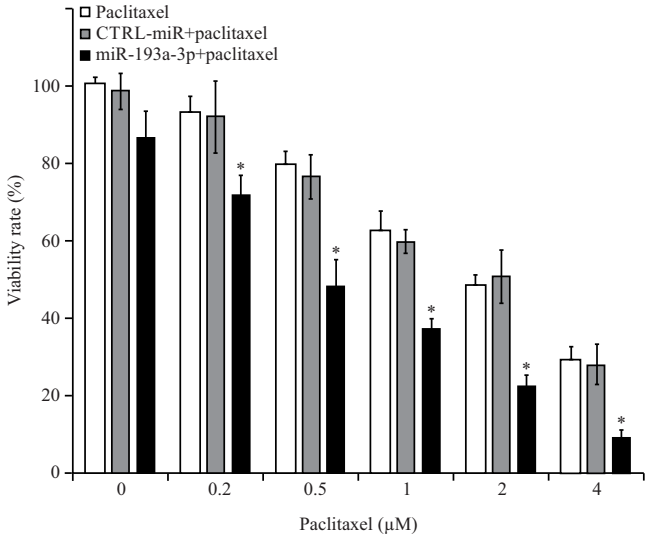


Fig. 2: Effect of miR-193a-3p on the chemosensitivity of A549 cells to paclitaxel

Cytotoxic effects of miR-193a-3p, CTRL-miR, paclitaxel and their combination were determined by MTT assay as described in the methods section. The data represent Mean±SD (n = 4), *p<0.05

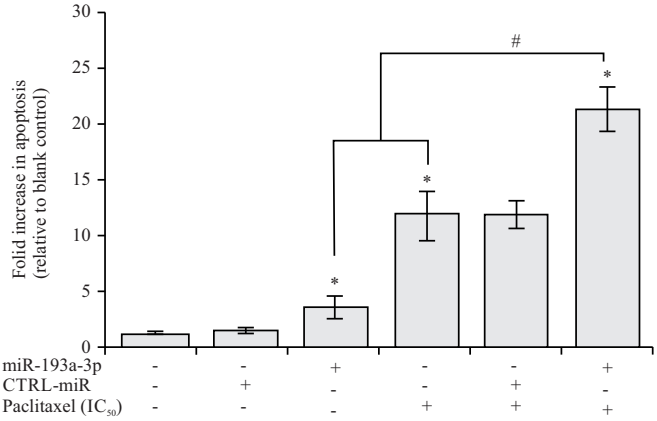


Fig. 3: Effect of miR-193a-3p overexpression on paclitaxel-induced apoptosis

Cells were transfected with miR-193a-3p and paclitaxel alone or in combination, 48 hrs after transfection, apoptosis was detected by cell death ELISA assay as described previously. The data represent Mean±SD (n = 4), *p<0.05 versus blank control

miR-193a-3p in A549 cells. Therefore, overexpression of miR-193a-3p showed efficient miR-193a-3p mimic transfection in A549 cells.

**miR-193a-3p increased the anti-proliferative effects of paclitaxel on A549 cells:** MTT assay was used to investigate the anti-proliferative effects of paclitaxel, alone or in combination with miR-193a-3p. Our results showed that paclitaxel exerted a potent dose-dependent inhibitory effect on the proliferation of A549 cells (Fig. 2). The $IC_{50}$ value for paclitaxel in A549 cells was 1.52 μM. More interestingly, a combination of miR-193a-3p with paclitaxel significantly increased the inhibitory role of paclitaxel on A549 cells. Cells treated with the combination of miR-193a-3p and 0.2-4 μM paclitaxel exert more potent anti-proliferative effects on A549 cells in compassion to paclitaxel treatment, alone ($p<0.05$, Fig. 2).

**miR-193a-3p potentiated the pro-apoptotic impact of paclitaxel on A549 cells:** For approving the MTT assay results, which showed that the miR-193a-3p combination enhanced the anti-proliferative function of paclitaxel, the effects of this combination were also evaluated on the A549 cells apoptosis. For this purpose, cells apoptosis was assessed by ELISA assay and measuring the mRNA expression levels of two important mediators of apoptosis, caspase-3 and caspase-9. As shown in Fig. 3, A549 cells treated with both paclitaxel and miR-193a-3p, alone, led to a significant increase in cellular apoptosis in comparison to control cells without any interventions ($p<0.05$). Moreover, apoptosis rate in cells treated with a combination of miR-193a-3p with paclitaxel was significantly higher in comparison to cells treated with miR-193a-3p and paclitaxel alone ($p<0.05$, Fig. 3).

In the next step, the expression levels of caspase-3 and caspase-9 were also measured. The results from the qRT-PCR analysis showed that miR-193a-3p mimic alone could not significantly increase the mRNA expression levels of both caspases ($p>0.05$, Fig. 4a-b). In addition, paclitaxel significantly overexpressed the mRNA levels of caspase-3 and caspase-9 in comparison to control ($p<0.05$, Fig. 4a-b). More importantly, a combination of miR-193a-3p with paclitaxel exerted a more potent effect in the increase in the expression levels of both caspases, when compared to mono treatments ($p<0.05$). Therefore, our results showed that miR-193a-3p can efficiently increase the paclitaxel-induced apoptosis in A549 cells.

**miR-193a-3p combination with paclitaxel suppressed cellular migration in A549 cells:** We also evaluated the effects of miR-193a-3p transfection on the paclitaxel-mediated suppression of cellular migration by measuring the mRNA levels of three key genes involved in the cellular migration including MMP-9, vimentin and ROCK. We found that A549 cells transfection with miR-193a-3p mimics significantly down regulated the expression levels of all three genes, as

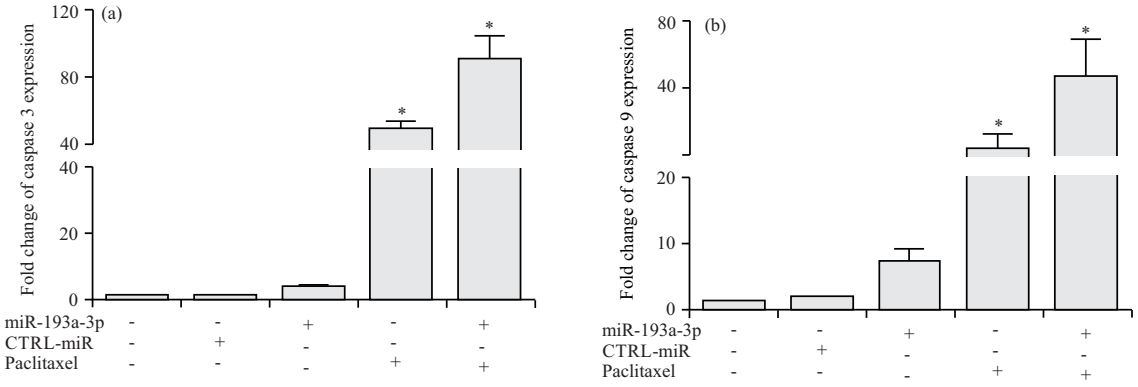


Fig. 4(a-b): (a) Caspase-3 and (b) Caspase-9 gene expression change 24 after transfection
Results were expressed as the Mean±standard deviation of experiments (n = 4), *p<0.05

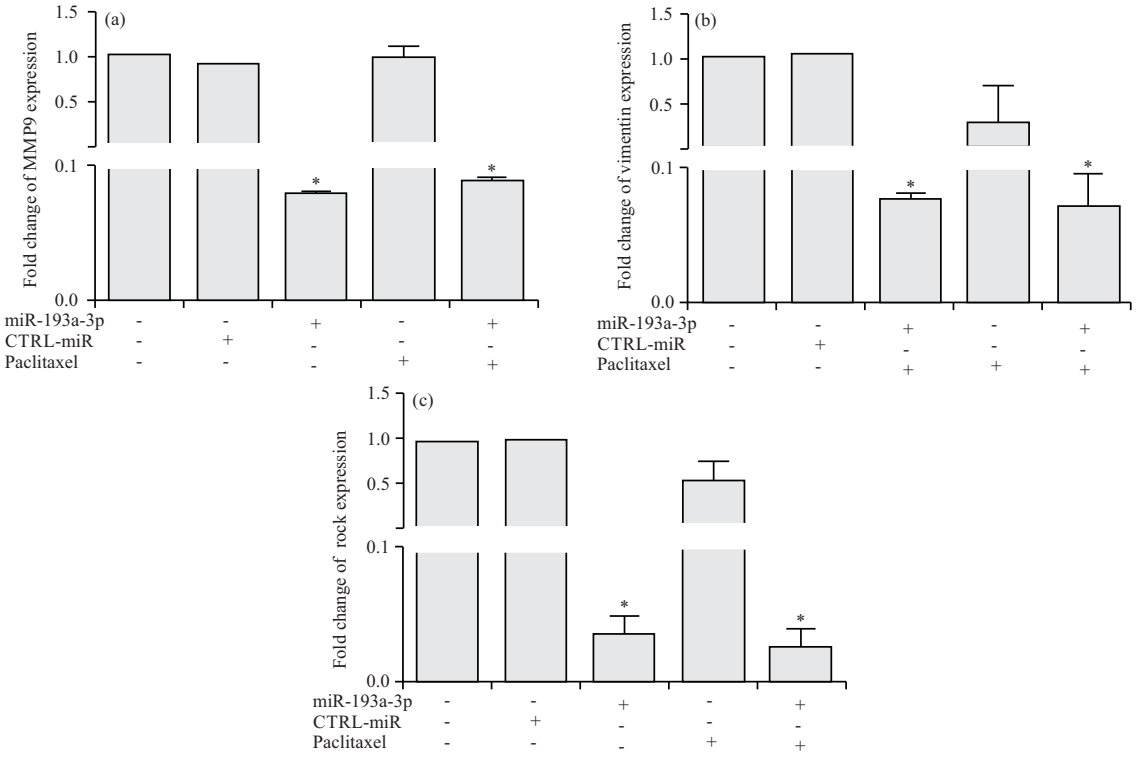


Fig. 5(a-c): miR-193a-3p alone or in combination with paclitaxel inhibited cell migration in A549 cells by downregulation of metastasis genes. qRT-PCR results showed that (a) MMP-9, (b) Vimentin and (c) ROCK were down-regulated in miR-193a-3p transfected cells compared to negative controls and paclitaxel
Results were expressed as Mean±standard deviation (n = 4), *p<0.05

compared to controls (p<0.05, Fig. 5a-c). Paclitaxel failed to exert a significant inhibitory effect on the expression levels of MMP-9, vimentin and ROCK (p>0.05). However, a combination of miR-193a-3p with paclitaxel resulted in a significant decrease in expression levels of all three genes, which means that miR-193a-3p overexpression in A549 cells increases the efficacy of paclitaxel in inhibiting cell migration.

## DISCUSSION

In this study, we showed that miR-193a-3p overexpression in A549 cells enhanced the chemosensitivity of cells to paclitaxel through increasing its anti-proliferative and pro-apoptotic effects, as well as downregulating key genes involved in the cellular migration. The development of

resistance against conventional chemotherapeutic agents, which increases the risk of tumour recurrence and decreases the survival rates of cancer patients, enhances the importance of investigating the drug resistance underlying mechanisms in various cancer types[27]. Currently, Some mechanisms of drug resistance in cancer cells generally include changes in drug metabolism, overexpression of drug transporters, inhibition of apoptosis, increased cancer stem cells and DNA repair capacity, abnormal miRNA expression, epithelial to mesenchymal cell transformation and cell invasion[27].

In this regard, an accumulating number of recent studies have demonstrated that dysregulation in the expression levels of tumour suppressor or oncogene miRNAs plays a critical role in the development of drug resistance. miR-193a-3p is a tumour suppressor miRNA with frequently reported down-regulated expression patterns in patients with NSCLC[28]. This miRNA also has major regulatory roles in the various aspects of NSCLC biology such as cellular proliferation, apoptosis, angiogenesis and metastasis[29-31]. Recently, studies have indicated that miR-193a overexpression in cancer cells can reverse drug resistance against chemotherapeutics in various cancer cells[32-34]. For example, Hejazi *et al.*[35] reported that miR-193a-3p transfection in colorectal cancer cells significantly increased the anti-proliferative effects of Taxol through inducing apoptosis in these cancer cells[35]. In another study, Haiyan *et al.*[36] showed that miR-193a was significantly downregulated in chemoresistant osteosarcoma cells and the introduction of this miRNA to resistant cells resulted in the complete reversal of chemoresistance through induction of apoptosis[36]. In similar, our results showed that miR-193a-3p resulted in a significant increase in the chemosensitivity of A549 NSCLC cells to paclitaxel through increasing apoptosis and overexpressing apoptosis key mediators including caspase-3 and -9.

EMT is demonstrated to have crucial roles in the cancer cells metastasis and development of drug resistance[37]. EMT is defined as acquiring mesenchymal features by cancer cells, hence migration and invading these cells to other organs[37]. Therefore, we also investigated the effects of miR-193a-3p transfection on the expression levels of key EMT-related genes matrix metalloproteinase (MMP)-9, vimentin and ROCK in A549 cells. We found that the expression levels of MMP-9 decreased in miR-193a-3p-transfected and paclitaxel treated cells. MMP-9 is an important protein in degrading the Extracellular Matrix (ECM) and tumour invasion and metastasis[38]. Wei *et al.*[39] reported that miR-26b suppressed NSCLC invasion and metastasis through inhibiting MMP-9. Wang *et al.*[40] also demonstrated that miR-424 regulated radiosensitivity through targeting MMP-9 in NSCLC. Furthermore, vimentin, which is a key component of intermediate filaments, is reported to be involved in NSCLC cells metastasis[40]. Another important gene with crucial functions in EMT and cancer cells invasion is ROCK encoding a Rho-associated serine-threonine protein kinase. Previous studies have reported that suppressing the expression levels of vimentin and ROCK was effective in inhibiting NSCLC invasion and metastasis[41-43]. Inconsistent with these studies, our results showed that miR-193a-3p mimics downregulated the mRNA expression levels of vimentin and ROCK in A549 cells. Taking together, these findings approve our hypothesis about the efficacy of miR-193a-3p transfection in increasing the chemosensitivity of A549 cells to paclitaxel by increasing apoptosis and inhibiting the expression levels of key EMT related genes.

## CONCLUSION

In conclusion, our results showed that miR-193a-3p restoration in A549 NSCLC was effective in reversing cancer cells resistance to paclitaxel. miR-193a-3p is a tumour suppressor miRNA, downregulation of which is related to poor prognosis and response to chemotherapy. Therefore, overexpression of miR-193a-3p may be a highly efficient strategy to preventing the development of drug resistance and increasing therapy efficiency. However, further studies need to elucidate mechanisms underlying the positive impact of miR-193a-3p upregulation on combating NSCLC.

## SIGNIFICANCE STATEMENT

This study discovers the miR-193a-3p restoration in A549 NSCLC was effective in reversing cancer cells resistance to paclitaxel which can be beneficial for Lung cancer clinical research. This study will help the researcher to uncover the critical areas of overcome drug resistance in the treatment of lung cancer that many researchers were not able to explore. Thus a new theory on miR-193a-3p is a tumour suppressor miRNA may be arrived at.

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