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Exploring Cytotoxic and Apoptotic Effects of Rosuvastatin on Lung Cancer Cell Line

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Abstract

Objective: This study aimed to investigate the efficacy of Rosuvastatin (Ros) in inhibiting lung cancer cell proliferation in compared to standard treatment, doxorubicin (Dox).

Methods: A549 cells were divided into four groups (untreated (control), Dox-treated, and Ros-treated cells) and subjected to six concentrations of the tested drugs. After 72 hours, the cytotoxicity and IC50 concentrations of each drug were determined. A549 cells were then subjected to the IC50 concentrations of either Ros or Dox or left untreated. The cell pellets were tested for caspase 3. Acridine orange/ethidium bromide stain was used to visualize and calculate apoptotic cells.

Results: Our results indicated that Ros treatment caused a significant decline in percentage of cellular growth when compared to control group with an IC50 of 45.24 µg/ml. While for Dox treated cells, only the highest concentration produced a significant reduction in percentage of cellular growth compared to control, with an estimated IC50 of 294.2 µg/ml. Furthermore, Ros caused a significant elevation in caspase 3 level compared to control. The same effect was nearly observed in Dox-treated cells with no significant difference between them. Additionally, cells treated with Ros exerted a higher percentage of apoptosis compared to control. For Dox treated cells, the percentage of apoptosis was lower than that of Ros, however; this effect was statistically non-significant.

Conclusion: Our findings confirmed that rosuvastatin suppressed the growth of lung cancer cells by triggering apoptosis via a caspase 3 dependent mechanism.

Keywords: Rosuvastatin, anticancer, lung cancer, caspase 3

Introduction

Lung cancer is one of the most common cancers and the most important cause of cancer-related death. The prevalence and mortality rates of lung cancer have increased dramatically during the last decades.[1] From a histopathological view, non-small cell lung cancer (NSCLC) accounts roughly for >80% of all lung cancers cases.[2] Although molecular targeted medicines and immunotherapies for NSCLS have improved 5-year survival rates, resistance to existing treatments is common.[3,4] Since intrinsic or acquired resistance and toxicity limit the clinical use of cytotoxic medicines, several novel therapeutic options are currently being considered for lung cancer. Lung cancer treatment has been made clearer by a deeper comprehension of the molecular principles underlying cytotoxic drug action, and new drugs that specifically target intracellular pathways linked to the unique characteristics of cancer cells are still being developed.[5,6] According to recent researches, the build-up of cholesterol is thought to be a significant contributor to tumor resistance. Cancer cells, such as those found in NSCLC, hepatocellular carcinoma, and breast cancer, consistently have higher cholesterol levels.[7] Hydroxy-3-methylglutaryl Coenzyme Reductase (HMGCR) is a rate-limiting enzyme that is necessary for the synthesis of endogenous cholesterol.[8] In previous researches, HMGCR was found to be up-regulated in different types of tumors, such as hepatic, pancreatic, and bladder, promoting the malignant phenotype of cancer cells.[9,10,2] Because cholesterol plays a role in cancer, inhibiting cholesterol synthesis by drugs, for instance statins- one of the HMGCR inhibitors- could be a therapeutic strategy to treat cancers. However, this effect has not been clearly reported in lung cancer. A study by Yuan et al. showed that cisplatin's effectiveness is significantly increased when HMGCR expression is knocked down, as this prevents lung cancer cell lines from proliferating, forming colonies, and migrating in vitro or in vivo.[11] Furthermore, statins use alongside chemotherapeutic drugs was found to limit their possible associated adverse effects like nephrotoxicity and cardiotoxicity.[12,13]

Doxorubicin (Dox) is an FDA-approved chemotherapeutic medication that is frequently used to treat a variety of malignancies, including lung cancer.[14] The principle anticancer mechanism of Dox includes induction of DNA damage by different mechanisms such as inhibition of topoisomerase 2 isozyme, free radical generation, and DNA-Dox complex formation. Reactive oxygen species (ROS) are created when the semiquinone radical of Dox intercalates between DNA base pairs. These species have the potential to cause lipid peroxidation and damage to DNA, which ultimately lead to apoptotic cell death,[15] where apoptosis regulation is critical for normal growth, homeostasis, and cancer therapy, and disruption of normal apoptosis induction can cause inappropriate cell growth, excessive cell division, and mutation accumulation. Therefore, control of apoptosis plays a vital role in cancer treatment.[16,17]

Regarding lung cancer treatment, nevertheless; a Dox-based regimen only yields an overall response rate of 30% to 50% in advanced NSCLCs, and the majority of patients develop resistance to Dox treatment.[18]

One strategy to hasten the clinical application of any agent in certain diseases is drug repositioning. The aim is to benefit from the fact that licensed pharmaceuticals have been studied on humans and comprehensive pharmacology, toxicology, and

formulation data are readily available. It can greatly save the time and expenses required to apply required treatments available on the market.[19]

Thereby, the goal of this study was to explore the anti-proliferative and apoptotic effects of Rosuvastatin (Ros), and comparing it to doxorubicin as a positive control agent on lung-cancer cell line.

Methodology

Chemicals and Cell Line

A549 lung cancer cells were obtained from Basrah's Iraq Biotech Cell Bank Unit.

Drugs and Chemicals: Doxorubicin (Zydus Pharmaceuticals, USA), Rosuvastatin (Pioneer, Iraq), Dimethyl sulfoxide (DMSO), 10% fetal bovine serum (FBS), MTT (3-(4,5 dimethylthiazole-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) powder, phosphate buffer saline (PBS), Acridine orange (AO) dye, Ethidium bromide (EB) dye, RIPA buffer (Sigma-Aldrich, USA), Roswell Park Memorial Institute-1640 (RPMI-1640) (Gibco, USA), Trypsin- EDTA solution (Capricorn, USA), Trypan-blue stain (Flow Laboratories, UK), Benzyl penicillin, streptomycin (Troge, Germany), Human caspase 3 ELISA kits (Elabscience, China).

Cytotoxicity (MTT) Assay

The A549 cell lines were extracted using trypsin-EDTA as a proteolytic agent, PBS as a washing agent, and FBS as a trypsin-deactivating agent. The cells were subsequently cultivated in a 96-well plate using RPMI-1640 liquid media with 100 units/ml streptomycin and 100 µg/ml benzyl penicillin. In order to facilitate the formation of a single layer of cells (80% growth phase), the samples were incubated at 37°C, 5% CO_2, and 95% humidity for 24 hours. Trypan blue stain was employed to determine the number of viable cells.[20] The previous medium was subsequently replaced with 200 µl of the medium, which included the test medicines and control group. Three groups were employed: control (untreated cells), Dox-treated cells, and Ros-treated cells. Six concentrations (including 800, 400, 200, 100, 50, and 25 µg/ml) were employed for each treated group, with four replicates for each concentration. The nonspecific conversion of formazan and the tested medications was assessed using a blank that contained only medium. The cells' viability was assessed after 72 hours of incubation using the (MTT) assay.[21] The percentage of viability was calculated as following:

$$\text{Viability\%} = \frac{\text{the optical density value of test well}}{\text{the optical density value of control well}} \times 100$$

The percentage of growth inhibition was calculated as following:

$$\text{Cell Growth Inhibition\%} = 100 - \left(\frac{\text{the optical density value of test well}}{\text{the optical density value of control well}} \right) \times 100$$

The dose-response curves were estimated using non-linear regression, which was based on a four-parameter logistic Hill equation. GraphPadPrism10 was employed to determine the concentration of drugs that producing a 50% decrease in cell viability (IC50) for each group.[22,23]

Measurement of Caspase 3 Level

Following seeding, A549 cells were treated with the resultant IC50 for 36 hours in three flasks, each containing three replicates (control, Dox-treated cells, Ros-treated cells). Following cell extraction and centrifugation, the supernatants were disposed of. The pellets were gathered, and lysis buffer were utilized to lyse the cells for proteins extraction, and later to measure caspase 3 with the ELISA test kits according to manual instructions.

Apoptosis assay Acridine Orange (AO)/Ethidium Bromide (EtBr) Double Staining

A549 cells were cultured at 4×10^4 cells/well in a culture plate and incubated for 24 hours at 37 C to achieve optimal confluence; then, the medium was discarded, and fresh medium was added containing IC50 concentration of the tested drugs. The cells were incubated for further 24 hours and the control left untreated. After that, cells were washed twice with PBS and stained with fluorescent stain (containing AO and EtBr). Then immediate examination and imaging under a fluorescence microscope was done.[24] The images were analyzed by ImageJ software 1.43 to calculate the total cell count, apoptotic cells and viable cells.[25] Then, the percentage of apoptosis were determined as following:

$$\text{Apoptosis\%} = \frac{\text{number of apoptotic cells}}{\text{total cells count}} \times 100$$

Statistical Analysis

Data were collected and analyzed using GraphPad Prism Edition 10. Significant differences in data means were assessed using two -way ANOVA and Dunnett's multiple comparisons test to analyze the results of the cytotoxicity assay. One-way ANOVA and LSD post hoc tests were utilized elsewhere. *P*-values of 0.05 or lower indicate a statistically significant differences.

Results

Effects of Rosuvastatin and Doxorubicin on Cell Growth

Our results indicated that almost all concentrations of Ros, apart from 25 µg/ml (800, 400, 200, 100, 50 µg/ml) caused a significant reduction in percentage of cellular growth ($P < 0.05$) when compared to the control group with an IC50 of 45.24 µg/ml. It is worthy to mention that the effects of Ros were not dose dependent since it approximately produced the same inhibitory effects with different concentrations apart from the lowest on (25 µg/ml). While for Dox treated cells, only the highest concentration (800 µg/ml) produced a significant reduction in percentage of cellular growth compared to control, with an estimated IC50 of 294.2 µg/ml. The data were illustrated in Figure 1.

The effects of Rosuvastatin and Doxorubicin on Caspase 3

In Ros treated cells there was significant elevation in cellular caspase 3 level (17.45 ± 2.2 ng/ml) compared to control (1.34 ± 0.01 ng/m), $P < 0.05$. The same effect was nearly observed in Dox-treated cells which showed significant increase in caspase 3 level (14.96 ± 6.88 ng/ml) compared to control, $P < 0.05$. While there was no significant difference between Ros and Dox treated groups, P value > 0.05. Figure 2.

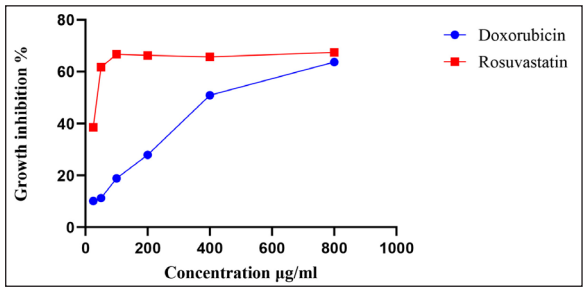

Fig. 1 **Dose-dependent cytotoxic effects of Rosuvastatin and Doxorubicin on A549 cell line.**

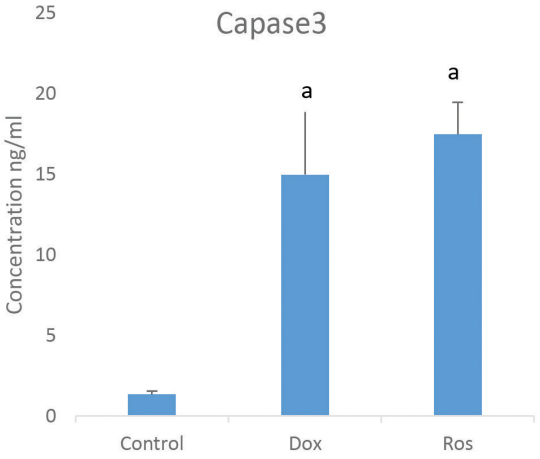

Fig. 2 **The effects of Rosuvastatin and Doxorubicin on the Caspase3 level in A549 cell line. a : significant from control.**

The Effects of Rosuvastatin and Doxorubicin on Apoptotic Assay

The A549 cell line's morphological changes were inspected with (AO/EtBr) under the fluorescence microscope. The results revealed that the control untreated cells were arranged in a well-organized structure and were green in color, but the treated cells displayed red fluorescence for late apoptotic cells and light orange for early apoptotic cells. Furthermore, a number of cells had experienced cell disintegration and necrosis Figure 3.

Cells treated with Ros exerted a higher percentage of apoptosis compared to control cells (51.9% vs 5.7% for Ros treated cells and control cells respectively), P value < 0.05. For Dox treated cells, the percentage of apoptosis (42.2%) was lower than that of Ros treated cells, however; this effect was statistically non-significant, P value > 0.05 Figure 4.

Discussion

Lung cancer is still one of the most frequent malignancies in the world, with significant mortality rates among both men and women.[1] Despite significant breakthroughs in treatment during the past decades, the 5-year survival rate is barely 18%.[26] Even though numerous approaches to treatment, such as chemotherapy, surgery, immunotherapy, radiotherapy, and targeted therapy, the mechanisms underlying treatment resistance in some types of lung cancer cells remain partially understood.[27,28] Recent studies have shown that statins can help prevent or treat cancer by interfering with critical cell activities like cell proliferation and differentiation. They cause cell death in many cell lines by two main mechanisms, which are apoptosis and necrosis.[29,30] The apoptosis induction is one of the functional mechanisms by which cytotoxic medications act and is critical for cancer treatment.[17] Statins' growth inhibitory and pro-apoptotic qualities have drawn interest for their potential use in the treatment of many malignancies, particularly lung cancer. This is why we examined the impact of rosuvastatin on lung cancer cell line.

Our results showed that Ros significantly inhibit cellular growth over a wide range of concentrations with relatively lower IC50 compared to Dox treatment that exerted a significant inhibitory effect only at the highest concentration with relatively high IC50 indicating resistance of the cells to Dox while exerted a higher sensitivity to Ros treatment.

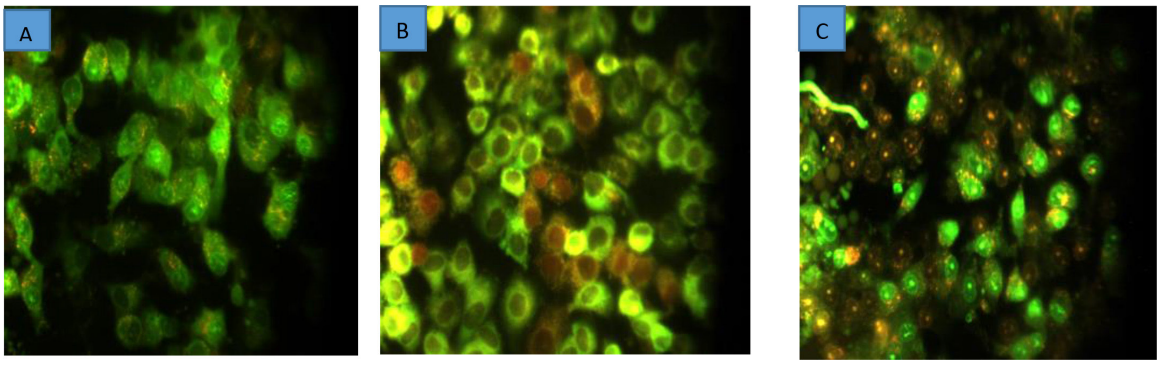

Fig. 3 **Visualization of apoptosis under fluorescence microscope. A: untreated cells. B, Dox-treated cells. C, Ros-treated cells. (AO/EtBr stain).**

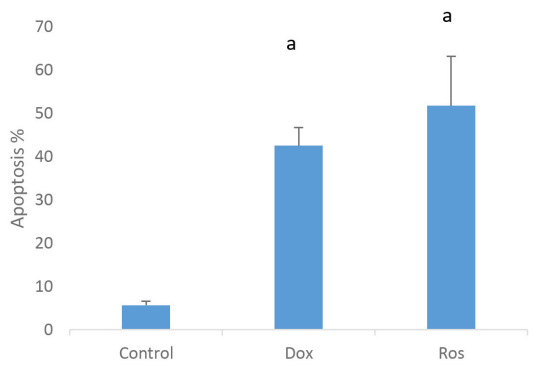

Fig. 4 **The percentage of apoptosis induced by Rosuvastatin and Doxorubicin in A549 cell line. a : significant from control.**

Regarding caspase 3 that belongs to the family of proteolytic enzymes called caspases, according to Kesavardhana et al. (2020), caspase-3 seems to be essential for the execution and activation of apoptosis among all the enzymes that are known to be involved in this process.[31] Since tumor cells primarily respond to chemotherapy by activating the caspase-3 and cell apoptosis pathways, caspase-3 has been identified as a crucial early biomarker for assessing chemotherapy-induced cell death.[32] Additionally, according to a study conducted on MCF-7 cell line, overexpression of caspase-3 appeared to improve chemosensitivity against acquired drug resistance.[33] Our results showed that Ros treatment was able to induce apoptosis in lung cancer cell line as reflected by increased caspase 3 level compared to control group. The apoptotic effect of Ros was validated and visualized by double staining with AO/EtBr stain. Cells were primarily yellow in the early stage of apoptosis, but in the late stage of apoptosis, cells were identified by an orange-red fluorescence stain. This distinction was gained by the capacity of acridine orange to permeate normal and injured cells, but ethidium bromide can only penetrate damaged cells and subsequently react with the DNA, displaying an orange-red color under the fluorescence microscope.

Our results run in alignment with a previous study by Zeybek et al who reported that Ros was able to induce apoptosis and activated caspase 3 in a thyroid cancer cell line.[19] It is worthy to mention that although the apoptotic effect of Ros was not statistically significant from that induced by Dox; however, it was achieved by a lower concentration of Ros than that of Dox, indicating a higher potency of Rosuvastatin.

Recently, a considerable body of evidence suggests that rosuvastatin has an anti-tumor activity against lung cancer. Liu et al. discovered that statin therapy dramatically reduced lung cancer risk in patients with chronic obstructive pulmonary diseases, and the impact was dose-dependent. Nonetheless, fluvastatin and lovastatin did not show any substantial reduction in the risk, while atorvastatin, simvastatin, pravastatin , and rosuvastatin considerably decreased this risk.[34]

Conclusion

In summary, our findings confirmed that rosuvastatin suppressed the growth of human NSCLC cells by triggering apoptosis via a caspase 3 dependent mechanism.

Conflict of Interest

None.

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