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New Perspective on the Action Mechanism of Doxorubicin in Breast Cancer- Overexpressions of miR-874-3p and miR-337-3p and Downregulation of STAT3 Gene

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Abstract

Background: Breast cancer is one of the common malignancies in women, for which doxorubicin (DOX) is widely used in its chemotherapy. Recently, it has been found that DOX affects the expression profile of oncogene genes and miRNAs. In this study, the impacts of DOX on the expressions of the STAT3 gene, miR-874-3p, and miR-337-3p were studied in the MCF-7 breast cancer cell line.

Methods: After exposure of MCF-7 cells with DOX, the MTT method was applied for evaluating the cell viability. Apoptosis and necrosis percentages were measured using flow cytometry. Also, the levels of ROS and NF-κB were measured in DOX-treated cells. Then, exosomes secreted from these cells were prepared. The shape of exosomes was studied by SEM. Finally, the expression of bax, bcl-2, p53, casp3, STAT3 gene, and miR-874-3p and miR-337-3p in MCF-7 cells as well as exosomes were evaluated using the RT-PCR technique. Data analysis was done by T-test in GraphPad Prism8 software.

Results: The exposure of MCF-7 cells to doxorubicin led to a concentration-dependent decrease in cell viability and increases in apoptosis and necrosis. ROS and NF-κB activity were increased in DOX-treated cells. In DOX-treated cells, decreased expressions of bcl-2 and STAT3 genes and overexpression of bax, p53, casp3, miR-874-3p, and miR-337-3p were observed compared to untreated control cells.

Conclusion: One of the mechanisms of the anti-breast cancer effects of DOX is the induction of changes in the expression of oncogenic genes, mediating by downregulating of STAT3 gene and overexpressing miR-874-3p and miR-337-3p. More studies are needed in this field.

Keywords: Breast cancer, Gene, miRNA, Doxorubicin

1. Introduction

Breast cancer includes almost a quarter of all malignancies in women, which has a high mortality rate (1). This malignancy originates from mammary tissues, covering cells, milk ducts, and lobules around the ducts (lobular) (2). Mutations in cancer-prone genes such as the breast cancer 1 and 2 genes (BRCA1 and BRCA2) are one of the most important causes of breast cancer, and the probability of developing this disease in people with these genetic mutations increases to 60% and 85%, respectively (3). The progress of breast cancer depends on various factors, including the type of tumor tissue, age, hormonal status, receptors, and genetic factors (4).

Currently, surgery combined with adjuvant treatment such a chemotherapy and radiation therapy is an approach that makes cancer patients survive (5).

Doxorubicin (DOX) is one of the antibiotics that are the most effective and widespread cytotoxic drugs in the treatment of tumors (6). The drug is administrated in a wide variety of cancers including breast, lung, stomach, thyroid, ovary, etc., and due to its chemical structure, it has high lipophilic properties

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and a long half-life in the body (7). DOX is a chemotherapy drug that inhibits the synthesis of DNA and RNA, inhibits topoisomerase II, and thus DNA degradation (7).

Disturbances in different signal transduction pathways are involved in the induction and promotion of cancer. One of these pathways is JAK/STAT signaling, which plays a pivotal role in various cellular functions such as proliferation and inflammatory response (8). This pathway can be connected to the membrane receptor and activated by different cytokines and growth factors. The cytoplasmic region of these receptors binds to the JAK protein and activates it. Phosphorylation of this protein leads to the binding of STAT and its activation and translocation to the nucleus. STAT is connected to the *MCL-1* promoter genes and leads to its expression (9). It has been found that signal transducer and activator of transcription 3 (STAT3) can have biomarker potential in malignancies (10) and its overexpression is associated with breast malignancy (11). The expression of STAT3 is affected by inflammation cytokines including interleukin 6 (IL-6) and interleukin 10 (IL-10) (12).

One of the regulatory elements involved in a variety of cellular signaling pathways in malignancy is miRNAs. Recently, it has been shown that miR-874-3p is downregulated in a variety of cancers, including breast (13), colorectal (14), hepatocellular carcinoma (15), and nasopharyngeal carcinoma (16), and its downregulation is associated with chemotherapy resistance (17). In osteosarcoma, miR-874-3p blocked cell migration by RGS4, and its expression was associated with reduced metastasis (18). Also, miR-337-3p has been shown to have a tumor cell suppressive role in ovarian cancer (19), and its downregulation leads to cervical cancer through Circ_0000388 (20). Interestingly, gastric cancer metastasis was correlated with the suppression of miR-337-3p expression (21) and it was found that its anti-metastatic action is done through targeting ARHGAP10 (22). The tumor growth inhibition role of this miRNA has been reported in other types of cancers including non-small cell lung (23) and cervical (24) cancers. Hence, miR-874-3p and miR-337-3p have important regulatory roles in miscellaneous cancers.

The current study aimed to evaluate the impacts of DOX on the expressions of miR-874-3p and miR-337-3p and target gene STAT3 in the MCF-7 cell line. Also, ROS content and NF-κB activity were evaluated in those cells. The expression levels of *bax*, *bcl-2*, *p53,* and *casp3* genes were studied in DOX-treated cells.

2. Materials and Methods

2.1. Cells preparation and cultivation

MCF-7 cell line was purchased from Pasteur Institute of Iran and cultured in DMEM culture medium containing 10% fetal calf serum (FBS), 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C and 5% CO_2.

2.2. MTT assay

When the cultured cells reached a surface density of 80%, the trypsinization was done and the cells were centrifuged at 1200 rpm for 5 min. Then, the supernatant solution was removed and the cell sediment was dissolved in 4 ml of culture medium. The cells (200 µl) were cultured in a 96-well plate and incubated at 37°C for 5 min. Then, DOX and MTT (20 µL, 5 mg/mL) were added to each well and the incubation was done according to the aforementioned conditions. Finally, cell absorbance was read at 490 nm wavelength by spectrophotometer.

2.3. Flowcytometry

Apoptosis and necrosis of MCF-7 cells were measured using the flow cytometry technique. For this purpose, 10^4 cells were placed in each well of a 96-well plate and the cells were treated with different concentrations of DOX. After 30 minutes, the samples were trypsinized and treated with annexin V and PI dyes. The samples were placed in the flow cytometry device.

2.4. Reactive oxygen species

For this purpose, the 2', 7' dichlorofluorescein diacetate method was used. After 30 min of treatments, MCF-7 cells were first trypsinized and transferred to PBS buffer containing 5.6 mM glucose and 2', 7' dichlorofluorescein diacetate (Merck, 10 µM) and incubated for 45 min. Then, the cells were centrifuged, and the supernatant was suspended in 1 ml PBS buffer. Finally, the fluorescent intensity was measured using a flow cytometer (BD, USA) at the excitation wavelength (485 nm) and emission wavelength (520 nm).

2.5. NF-κB

NF-κB activity was quantified using the ELISA technique using a kit (Trans-AM NF-κB; Active Motif, Carlsbad, CA) according to the manufacturer's instructions using p50 subunits antibodies.

2.6. Isolation of exosomes

To isolate exosomes, first, a portion of the culture medium was removed and centrifuged at 300xg for 15 minutes. Then, the removed supernatant was used to isolate exosomes using the Exoquick kit. All kit manufacturer's instructions were followed. A scanning electron microscope (SEM) was used to confirm the isolation of exosomes.

2.7. RNA extraction

To isolate RNA, 50 µL of Trizol was poured into the cell culture flask and incubated for 5 minutes. Then, 50 µL of the contents of the flask were transferred to the microtube and 15 µL chloroform was poured into it. Next, it was centrifuged at 12000xg for 10 min. The surface solution was removed and transferred to a microtube, and then isopropanol was added to it. After ten minutes, centrifugation was performed at 12000xg for 10 minutes. In the next step, the surface solution was removed and 1 ml of 75% ethanol was poured into it. Centrifugation was done again at 7500xg at 4°C and 30 µL of DEPC-treated water was added to the precipitate. The prepared RNA was kept at -80°C freezer. The quality and quantity of extracted RNAs were checked using a Nanodrop device and UV spectrophotometry methods, respectively.

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2.8. miRNA polyadenylation

For this purpose, 2 µL of total RNA, 1 µL of ATP (10mM), 4 µL of poly A polymerase buffer, 2 µL of poly A polymerase enzyme, and 6 µL of RNAase-free water were mixed in a tube and vortexed. Finally, the mixture was incubated for 10 min (37°C).

2.9. cDNA synthesis

At first, 2 µL of oligo dT (ZymAll oligo (dT)), 3 µL of polyadenylated template RNA, and 10 µL of RNase-free deionized water were poured into a microtube and incubated for 5 min at 65°C. Then, 4 µL of 5x reaction buffer, 2 µL of DTT, 1 µL of ribolock RNase inhibitor, 2 µL of dNTP, 3 µL of RTase rxn buffer, 1 µL of hyperscript RTase and RNase-free deionized water were added to it. This reaction mixture was incubated at 42°C for 30 min and then at 25°C for 5 min.

2.10. Real Time PCR

General reverse primer and forward primer specific for miR-337-3P and miR-874-3P were prepared by Exiqon kit. The primer sequences included: *STAT* gene: F-5'- CTTTGAGACCGAGGTGTATCACC-3' and R-5'- GGTCAGCATGTTGTACCACAGG-3'; *bax*: F-5'- TCAGGATGCGTCCACCAAGAAG-3 and R-5'- TGTGTCCACGGCGGCAATCATC-3'; bcl-2 F-5'- ATCGCCCTGTGGATGACTGAGT-3' and R-5'- GCCAGGAGAAATCAAACAGAGGC-3'; casp3: F-5'- GGAAGCGAATCAATGGACTCTGG-3' and R-5'- GCATCGACATCTGTACCAGACC-3'; p53: F-5'- CCTCAGCATCTTATCCGAGTGG-3' and R-5'- TGGATGGTGGTACAGTCAGAGC-3'; U6 snRNA and GAPDH control genes were used in the current study. The sequence of their primers was as follows:

GAPDH: F-5'- ACACCCACTCCTCCACCTTTG-3' and R-5'- TCCACCACCCTGTTGCTGTAG-3'

U6 snRNA: F-5'- CCGATAAAATTGGAACGATACAG-3' and R-5'- TCGARRRGTGCGTGTCATCCT-3'.

The temperature and time program for gene amplification in RT-PCR included 1 cycle of 95 °C for 5 min, 40 cycles of 95 °C for 5 s, 65-62 °C for 20 s, and 72°C for 30 s.

2.11. Statistical analysis

For the gene expression analysis, the $2^{-\Delta\Delta CT}$ method was applied. The data (mean ± standard deviation) were analyzed by T-test procedure at a significant level of $P<0.05$ by GraphPadPrism software.

3. Results

3.1. Cell viability

MCF-7 cells were exposed to concentrations of 0, 10, 20, 30, and 40 µM DOX, and the results showed that cell viability decreased with increasing drug concentration. At a concentration of 30 µM of the drug, MCF-7 cells showed 48.65±3.94 % viability. The IC_{50} of the drug on MCF-7 breast cancer cell lines was calculated at 31.4 µM (Figure 1).

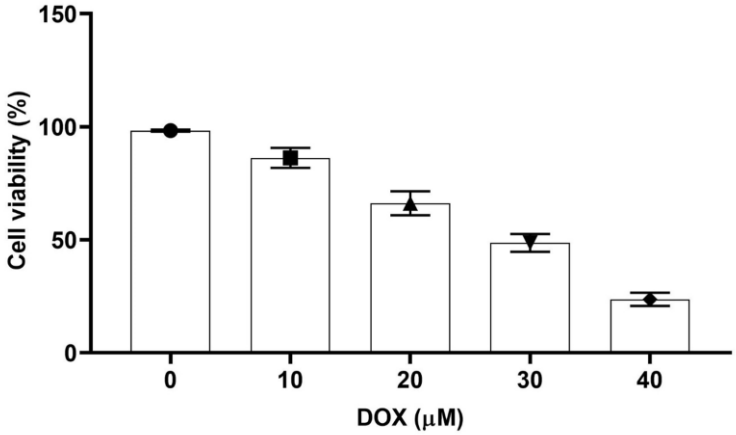


Figure 1. The DOX-treated MCF-7 cell line viability was measured by the MTT method. The cells were treated with DOX for 30 min (n=3).

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3.2. Apoptosis and Necrosis

Using the flow cytometry technique, we investigated the percentages of apoptosis and necrosis of MCF-7 cancer cell lines exposed to different concentrations of DOX, and the results indicated a concentration-depend increase in the apoptosis and necrosis of the cells. So, at the concentration of 40 μM of this drug, 48.11 ± 3.78% apoptosis (Figure 1a) and 28.22 ± 1.11% necrosis (Figure 1b) were observed in MCF-7 cells. Therefore, DOX led to the death of MCF-7 cells by stimulating apoptosis and necrosis.

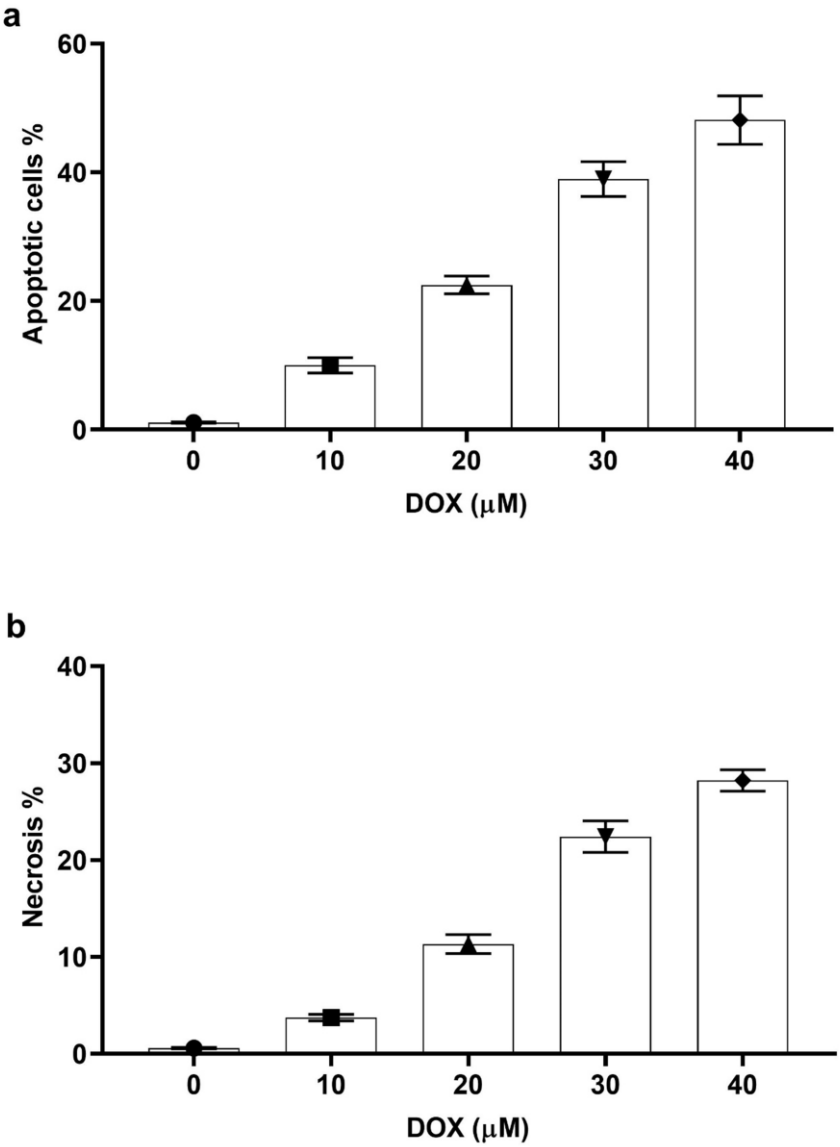


Figure 2. The apoptosis (a) and necrosis (b) percentages of DOX-treated MCF-7 cells were measured by flow cytometry technique. The cells were treated with DOX for 30 min (n=3).

3.3. Reactive oxygen species

DOX-induced ROS in MCF-7 cells in a concentration depend on manner. Although there was no significant difference in ROS content in 10 μM DOX-treated cells compared to the untreated ones, an overproduction of ROS was observed at a concentration of 20 μM and higher, and the highest content was obtained in cells treated with 40 μM DOX (Figure 3).

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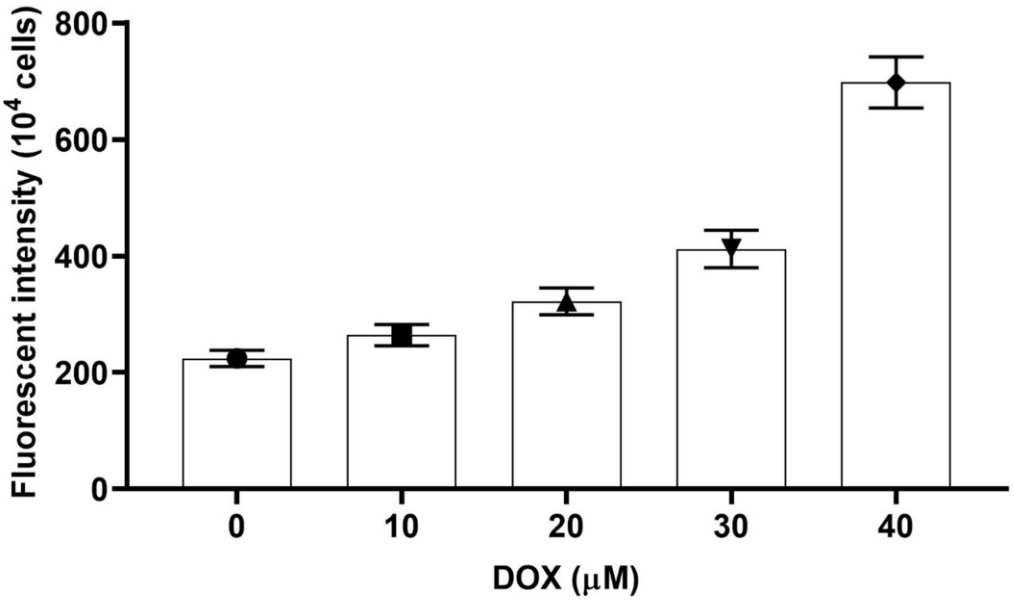


Figure 3. Reactive oxygen species (ROS) contents in DOX-treated MCF-7 cells (n=3).

3.4. NF-κB activity

The NF-κB activity was studied in MCF-7 cells exposed to DOX, and the results indicated an increase in this transcription factor with increasing DOX concentration in the medium. The NF-κB activities in DOX-exposed MCF-7 cells at concentrations of 10, 20, 30, and 40 μM were 15.32, 48.22, 89.40, and 86.2%, respectively (Figure 4).

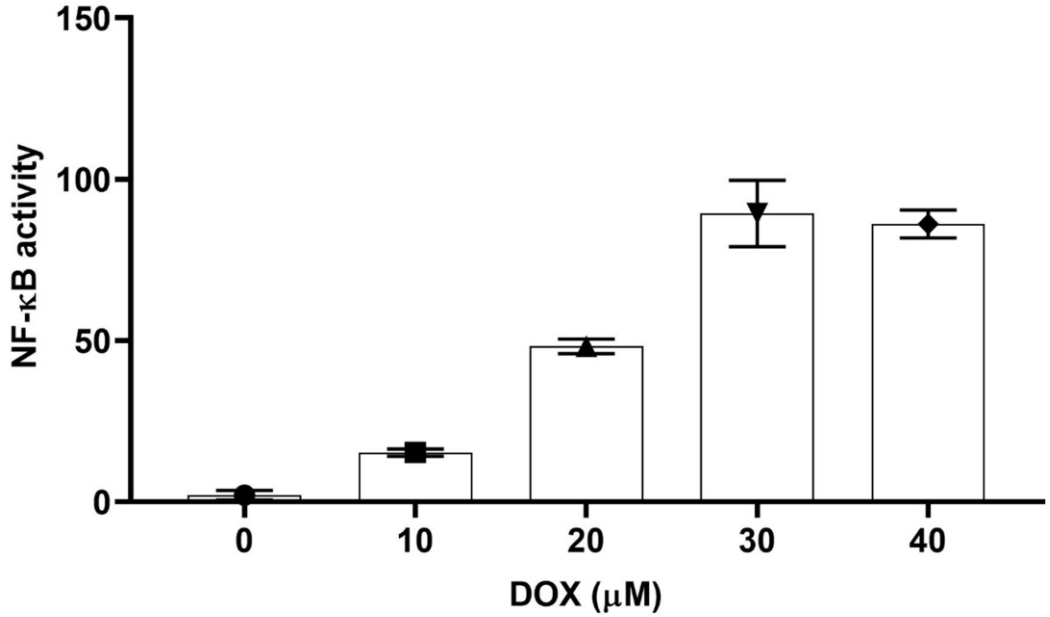


Figure 4. . Inhibition of NF-κB activity in the DOC-exposed MCF-7 cells (n=3).

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3.2. Gene expression analysis

bax, *bcl-2*, *p53* and *casp3*

Pro-apoptotic gens *bax*, *p53,* and *casp3* were significantly overexpressed in the MCF-7 cell line compared untreated control one. However, *bcl-2* downregulated in DOX-treated cells. The *bax* expression was increased ~3 times compared to control (p=0.003). This was the case for *p53* and *casp3* genes and both genes showed significant over expressions compared to control cells (Figure 5).

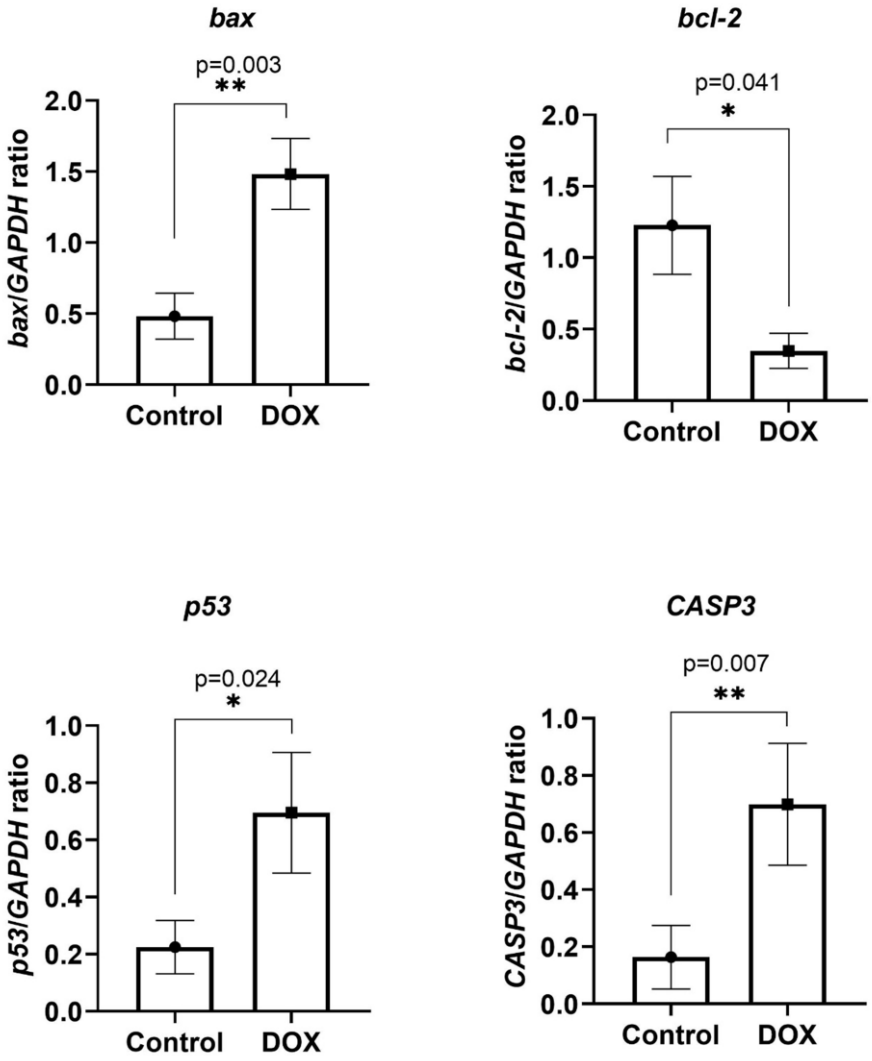


Figure 5. The expression levels of bax, bcl-2, p53 and casp3 genes in the DOX-treated MCF-7 cells (n=3).

miR-337-3p and *miR-874-3p*

Treatment of MCF-7 cells with DOX led to an overexpression of both *miR-874-3p* and *miR-337-3p* compared to untreated cells (control) (Figure 6, P<0.001). Therefore, DOX appears to exert anticancer effects in breast cancer by overexpression of *miR-874-3p* and *miR-337-3p*, which are both tumor suppressors.

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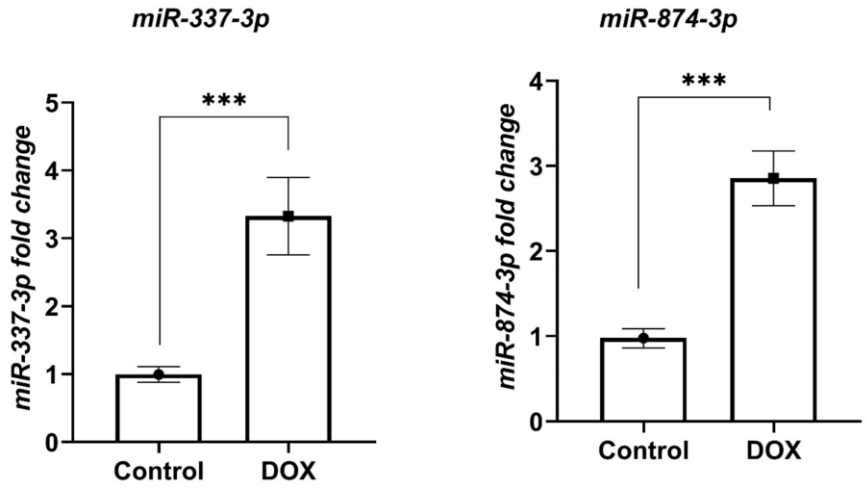


Figure 6. The expressions of miR-337-3p (a) and miR-874-3p (b) in untreated (control) and DOX-treated MCF-7 cells (n=3). ***: P<0.001 vs control.

The morphology of separated exosomes is shown in Figure 7. As can be seen, they are spherical with a size of 50 to 100 nm (Figure 7 above). We also measured the expression levels of *miR-337-3p* (Figure 7a) and *miR-874-3p* (Figure 7b) in exosomes separated from untreated and Dox-treated MCF-7 cell lines and results showed that DOX overexpressed both miRNAs in exosomes (Figure 7).

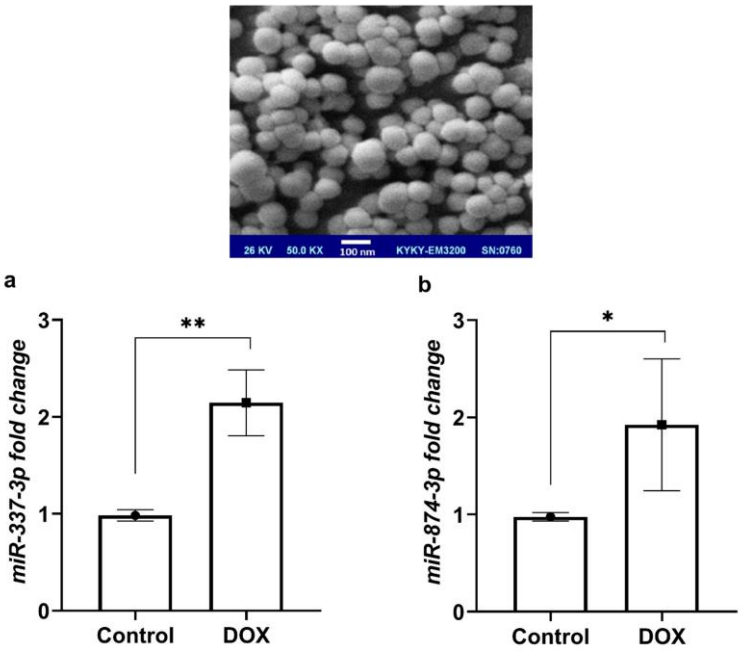


Figure 7. The morphology of separated exosomes from MCF-7 cell line treated with doxorubicin (above) and the expressions of miR-337-3p (a) and miR-874-3p (b) in untreated (and Dox-treated exosomes separated from MCF-7 cell line. *and **: P<0.05 and P<0.01 vs control, respectively.

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STAT3

STAT3 significantly downregulated in the Dox-treated MCF-7 cell line compared to control (P<0.05, Figure 8). Therefore, DOX appears to exert anticancer effects in breast cancer by downregulation of *STAT3*.

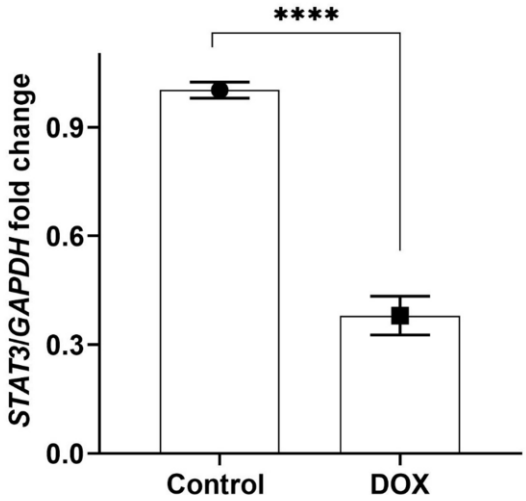


Figure 8. The expressions of *STAT3* gene in untreated and Dox-treated exosomes separated from MCF-7 cell line. ****: P<0.0001 vs control.

4. Discussion

The results indicated that the IC_{50} of DOX on MCF-7 cancer cells was 31.4 μM. Also, The DOX-treated MCF-7 showed upregulations of *bax*, *p53*, *casp3*, *STAT3* gene, and overexpressions of both *miR-874-3p* and *miR-337-3p* in MCF-7 cells and exosomes separated from them. However, *bcl-2* gene expression was decreased in the MCF-7 cell line.

The exposure of MCF-7 cells to the DOX led to a reduction in cell viability in a dose-depend manner, which is consistent with the findings of other studies (25, 26). The action mechanism of DOX on MCF-7 cells is attributed to the activation of cell apoptosis and the change in the expressions of genes involved in apoptosis, such as downregulations of the *bcl-2* and overexpression of the *bax* gene. For example, when MCF-7 cells treated with DOX, Eskiocak et al. (2008) found that the drug had inhibitory effects on telomerase activity by downregulating the *bcl-2* and overexpressing the *bax*, leading to apoptosis of MCF-7 cells (25). We also measured the expressions of *p53* and *casp3* genes in DOX-treated MCF-7 and results showed upregulations of both genes. *p53* and *casp3* have pro-apoptotic roles and their overexpressions indicated apoptosis. Therefore, the cytotoxicity of DOX on MCF-7 cells in the present study can be attributed to the apoptosis pathway activation, causing cell death.

Both NF-κB and ROS contents were increased in DOX-treated MCF-7 cells compared to untreated cells. This drug is known as an agent that causes ROS by redox activation (27), and the side effects of this drug, such as cardiotoxicity, can be attributed to this characteristic of DOX (27). In the present study, the ROS content of the MCF-7 cells was increased by increasing the concentration of the drug, which can explain the mechanism of DOX toxicity on cancer cells and the induction of apoptosis (28). Oxidative stress caused by DOX can activate the NF-κB pathway (29), playing a pivotal role in proliferation and immune response (30). The NF-κB overexpression was correlated with the cells' apoptosis induction (31), and in the present, research it was found that ROS overproduced and NF-κB overexpressed in DOX-treated cells. Therefore, the action mechanism of DOX-induced apoptosis in the cells can be attributed to oxidative stress induction and the subsequent increase in NF-κB levels.

As mentioned, one of the pathways involved in tumorigenesis is the JAK/STAT signaling pathway, the activation of STAT and its transfer to the nucleus leads to the transcription of oncogenes (4). *STAT3* has been found to overexpress in miscellaneous tumors such as breast cancer, so it has the potential to be used as a biomarker in this malignancy. In the present study , the DOX was able to reduce the expression of the *STAT3* gene, which is of great importance. In a study, it was shown that downregulation of STAT3 can lead to increased sensitivity of tumor cells to the DOX (32). On the other hand, in neuroblastoma, it was shown that resistance to this drug is caused by the activation of STAT3 by factors secreted by cancer cells and as a result inhibiting apoptosis (33). Therefore, it seems that there is a close relationship between the *STAT3* gene expression and the cancer cells' resistance to the DOX (34), and in the present study it was shown that the treatment of MCF-7 cells with DOX leads to downregulation of *STAT3*. This can prevent the expression of oncogenes in cancer cells and thus prevent the progression of cancer.

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Both miR-874-3p and miR-337-3p have antitumor roles in many cancers, and their blocking is accompanied by cancer progression and metastasis. In the present study, it has been shown that DOX-treated MCF-7 cells showed significant overexpression of both *miR-874-3p* and *miR-337-3p* compared to untreated cells, which can indicate the potential of this drug in preventing the progression of breast cancer. The role of miRNAs in inducing resistance or sensitivity of cancer cells to DOX has been shown in many studies (35, 36). For example, the treatment of gastric cancer with DOX led to the overexpression of miRNA-520 h, thereby increasing the sensitivity of cancer cells to the drug (35). Also, the treatment of breast cancer cells with DOX increased the expression of miRNA-15a and miRNA-16 and led to high sensitivity of cells to doxorubicin (37). Therefore, there is a close relationship between DOX and changes in the expression of miRNAs and exerting cytotoxic effects on tumor cells. In the current research, it was also shown that both *miR-874-3p* and *miR-337-3p* overexpressed in DOX-treated cells, and since both of these microRNAs have antitumor functions, therefore, it can be concluded DOX exerts cytotoxic activity on breast cancer cells by inducing the expression of miR-874-3p and miR-337-3p.

The present study provides a new perspective on the mechanism of action of DOX in breast cancer by changing the expression of the *STAT3* gene and miR-874-3p and miR-337-3p, which is one of the innovations of the present research. Nevertheless, the study has been conducted in vitro, and the confirmation of the results requires further investigations, and in vivo studies on animal models are recommended. More studies are needed in this field.

5. Conclusion

In general, it is concluded that DOX exerts cytotoxic effects in breast cancer by downregulating *STAT3* and *bcl-2* and the overexpressing of *bax*, *p53*, *casp3*, miR-874-3p, and miR-337-3p. However, more studies are needed on the action mechanism of this drug and the changes in gene expression profile.

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