Original Article

Overcoming Drug Resistance in Breast Cancer Using Quercetin Nanodrugs

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Abstract

Background & Objective: Breast cancer is one of the most common cancers in the world. Treatment methods for this disease have been with poor results. In recent years, more attention has been paid to stem cells due to their cytotoxic properties. According to previous results, the effect of nanoquercetin on breast cancer cells in this study was used concomitantly with doxorubicin, which is a chemotherapy drug and in some patients has therapeutic resistance.

Materials & Methods: The above study was performed on MCF7 and BT474 human breast cancer cells. Quercetin was synthesized, then different concentrations of 10, 20, 40, 80 and 160 of quercetin and 1, 2.5, 5 and 10 µg/ml of doxorubicin were prepared and two cell lines were treated for 24 h. MTT test was used to determine cell viability and flow cytometry test was used to determine the extent of apoptosis in both cell lines.

Results: The results showed that MCF7 and BT474 cells that were affected by quercetin and doxorubicin, increasing the concentration of quercetin and doxorubicin decreased the survival of both cell lines within 24 h. The LC50 concentration was calculated for both cells treated with nanoquercetin 40 µg/ml and for doxorubicin (0.1 mg/mL). The results also showed that in both cell lines, an increase in cellular apoptosis occurred after incubation with quercetin and then incubation with doxorubicin.

Conclusion: Comparison of doxorubicin (DOX), quercetin (QU) and quercetin and doxorubicin (QU-DOX) groups with controls shows that with the presence of quercetin-doxorubicin, it had a greater inhibitory effect on cancer cells.

Keywords: Quercetin, Doxorubicin, MCF-7, BT474, Breast Cancer

Introduction

Cancer is a global and growing problem that appears in different forms (1, 2) and has a high rate in developed countries because not only it has demographic changes but also changes in risk factors, thereby the consequences of globalization of economies. Behaviors increase the existing burden of cancers. Breast cancer is the most common type of cancer among women (3-5). Breast cancer is a type of cancer that starts in the breast tissue and only a small part of the breast cancer cells has the ability to produce new tumors, and it is easy to tell from the surface signs of the cells that they are cancerous. In the United States, about 40,000 deaths occur annually. These breast tumors include a diverse population of cancer cells in terms of phenotype (6, 7). Common treatments for breast cancer include surgery,

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radiation therapy, chemotherapy, hormone therapy, and biological therapies, depending on the progression of the cancer, its type, and physical condition. The patient is different in different people. Cancer treatment is local or comprehensive. (8) Today, targeted treatment with nanoparticles is done. Nanotechnology has the potential to bypass several forms of conventional therapeutic formulations. In fact, significant steps have been taken in the use of engineered nanomaterials to treat cancer with high properties, sensitivity and efficiency. Nanomaterials made with specific ligands can target cancer cells in a predictable manner and deliver encapsulated loads effectively. In addition, nanomaterials can also be designed to increase drug loading, improve body half-life, controlled secretion, and selective distribution by changing their composition, size, morphology, and surface chemistry (9, 10). Over the past ten years, quercetin has been explored in many applications due to its remarkable conductivity, thermal properties, and mobility of carriers. Numerous studies have been conducted to discover the properties of quercetin, which allows more than one activity to be performed and combines multidrug systems with photothermal therapy, indicating that quercetin is an attractive tool for overcoming barriers to cancer treatment. Quercetin belongs to the flavonoid family, which has antioxidant activities in many plants, including fruits, vegetables, green tea, and even red wine. This supplement is available on the market as a dietary supplement and has physiological health effects (11, 12). Quercetin's name, derived from 1857 from Questum (oak forest), is a natural inhibitor of polar auxin transport. Quercetin is one of the most abundant flavonoids in the diet. With an average daily intake of 25 to 50 mg, it can even be obtained. Quercetin has anti-inflammatory, anti-cancer and anti-prostate activities along with its beneficial effects on high cholesterol, kidney transplantation, asthma, diabetes, viral infections, lung, schizophrenia and cardiovascular diseases. It also has the potential to deplete hydroxyl radicals (OH^-), hydrogen peroxide (H_2O_2) and superoxide anion (O^{-2}). In proteins, amino acids, DNA lead to epigenetic changes. Quercetin has the ability to combat these harmful effects. ROS plays an important role in the progression of Alzheimer's disease (AD) and it is suggested that quercetin is the best option for overcoming cellular and molecular signals in regulating normal physiological functions. The protective neuroprotective effects of quercetin are mainly due to the potential increase or decrease in the regulation of cytokines by nuclear factor (ereotrost2) such as (paraxonase2, Nrf2) c-Jun N-terminal kinase (JNK), protein kinase C, the signal cascades are Mitogen-activated protein (MAPK) and PI3K / Akt pathway (13, 14). In this project, quercetin is studied in the form of a nano-drug with the aim of affecting breast cancer stem cells along with doxorubicin as a chemotherapy drug.

Materials & Methods

Synthesis of Quercetin

In plants, Phenylalanine is converted to 4-coumaryl-CoA as a series of steps known as the general phenylpropanoid pathway using Phenylalanine ammonia lyase, Cinnamate 4-hydroxylase, and 4-coumaryl CoA-ligase. A 4-Coumaroyl-CoA molecule is added to three Malonyl-CoA molecules to add Tetrahydroxychalcone using 7,2'-dihydroxy 4'-methoxyisoflavanol synthetase. Tetrahydroxychalcone is then converted to Naringenin using the calcon isomerase. Naringenin is converted to Eryiodictyol using the flavonoid 3-hydroxylase. Eriodictyol is then converted to Dihydroquercetin with flavonone 3-hydroxylase, which is then converted to quercetin using flavonol synthase. Like Rutin and Cocritrein, which are found in citrus fruits, buckwheat, and onions, quercetin is the Coccitrogen and Rutin Glucosides, respectively, along with Rhamnose and Rutinose. To make quercetin solution, 0.067g of quercetin (Fluka) was dissolved in 1 mL of DMSO (sigma) and 0.2 M solution was prepared. TEM electron microscopy (TEMKV 100 model: Leo 906 Zeiss, Germany) was used to determine the properties

of the prepared quercetin and DLS (Zeta Sizer: Maldon UK ZS series model) was performed to determine the particle size and dispersion of the particles.

Study grouping

In order to evaluate the anti-cancer effects of Quercetin and Doxorubicin and to evaluate cell viability, MTT, apoptosis and MCF7 and BT474 cancer cell tests.

- **Control group:** without any treatment.
- **The group I:** DOX
- **The Group II:** QU-DOX

Cell Culture

In this study, two categories of breast cancer cells (MCF7 and BT474) were used. The cells were frozen and delivered from the Iranian Genetic Resources Center and cultured in the laboratory on DMEM (Dulbecco's Modified Eagle Medium) medium. Cells in DMEM medium with 10% FBS serum supplementation were used as a complete culture medium for cells. Cells produce acidic metabolites as they grow, causing the culture medium to gradually change color from purple to yellow. For this reason, the cell culture medium is changed every 24 to 48 hours. When cell density reached 80%, cell passage was performed by adding Trypsin. To freeze the cells, the supernatant of the flask was drained, and then washed with PBS 1X. Cell isolation was performed physically at 37 ºC. The contents of the flask were poured into the Falcon containing the culture medium until the Trypsin activity ceased. The falcon containing the suspension was centrifuged at 1500 g for 6 minutes, then frozen in a microtube. Freezing medium contained 50% DMEM, 40% FBS, and 10% DMSO.

MTT Test

In this test, the measurement was based on exposing the cells to different concentrations of drugs (QU-DOX) and measuring the number of dead cells. For this purpose, the yellow active substance Tetrazolium and the formation of insoluble purple crystals of Formazan were used in the MTT method. In this method, 24 h after culturing the cells with the desired concentration, the surface culture medium of the cells was changed and the cells were cultured for 3 h with culture medium containing Tetrazolium dye. Then, the medium was combined using 100 µl of dimethyl sulfoxide and the amount and intensity of adsorption were read using an electrifier with a wavelength of 570 nm.

Evaluation of apoptosis by flow cytometry

Flow cytometry was used to evaluate the rate of apoptosis in MCF7 and BT474 cancer cell lines as a result of incubation with QU and then (QU-DOX) DOX compared to the control and DOX groups. After the relevant treatments, the cells were trypsinized, then centrifuged at 2000 rpm, followed by 5 ml of phosphate buffer. After re-centrifugation, add 1 mL of kit buffer and after severe pipetting, add 5µL of anxin and incubate for 4 minutes in a dark environment. Finally, 4µL of propidium iodide solution was added and analyzed by flow cytometry.

Results

Determination of Nanoquercetin Properties

Quercetin nanoparticles were prepared from graphite powder following Hammers method. The results revealed that the synthesized solution contained proper conditions in terms of physicochemical properties. According to the TEM image, Quercetin nanoparticles multilayer with a size of 2 µm was formed (Figure 1). The DLS diagram was used to determine the properties of Nanoquercetin. According to Table 1, the average particle diameter was 1302 nm.

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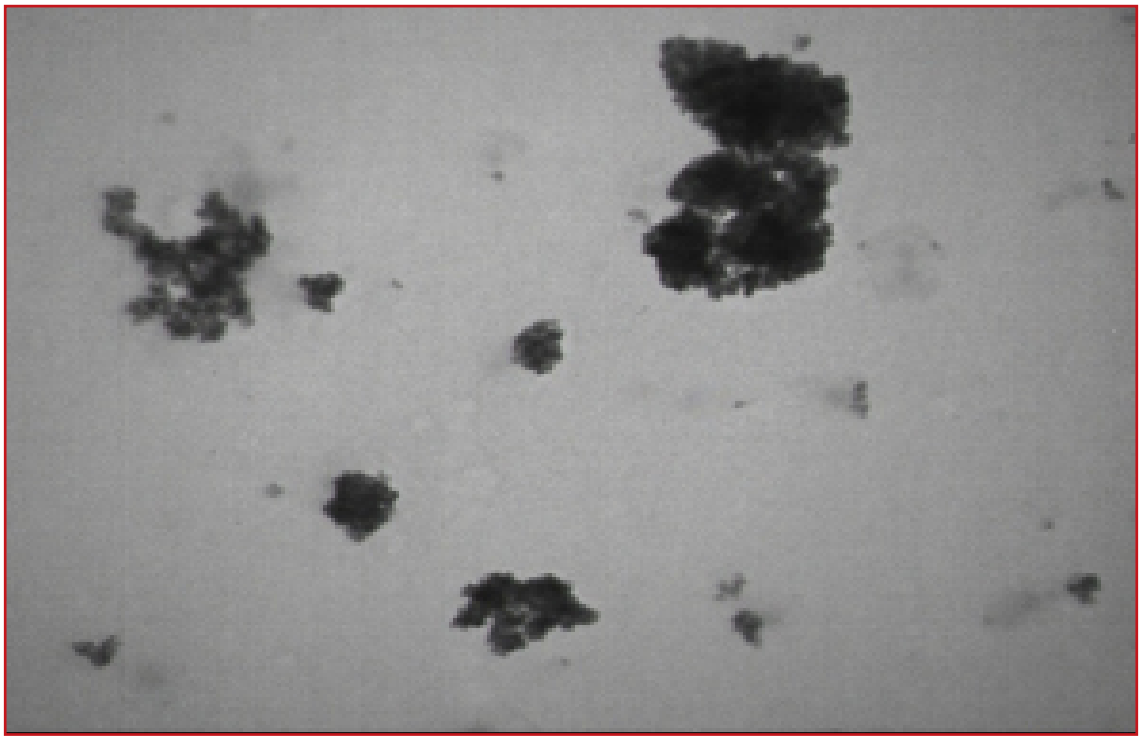

Figure 1. Microscope image of TEM Quercetin nanoparticles

Table 1. DLS analysis results showing the particle diameter and dispersion

Run	Eff. Diam.(nm)	Half width (nm)	polydispersity	Base line Index
1	560	239.8	0.183	0.0 / 90.54 %
2	1494	107.6	0.005	0.0 / 100. 00 %
3	915.7	376.1	0.167	2.5 / 100.00 %
4	1672	110.3	0.005	0.2 / 95.52 %
4	1871	140.3	0.005	5.5 / 95.52 %
Mean	1302.9	194	0.073	1.7 / 96.31 %
Std. Error	244.7	50.8	0.042	1.1 / 1.76 %
Combined	1017.4	154.2	0.062	6.8 / 96.32 %

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MTT Test Results

Different concentrations of 10, 20, 40, 80 and 160 µg/mL were used to evaluate the effect of quercetin on MCF7 and BT474 cells. The results showed that the survival rate of MCF7 and BT474 cells decreased with increasing quercetin concentration. The effect of quercetin on MCF7 and BT474 cancer line cells was significantly reduced after 24 h. There was also a significant difference between each cell line affected by quercetin and its control group, but there was a significant difference between the two lines in each concentration (Figure 2). MTT assay was used to determine the cell viability and doxorubicin LC50 concentration on MCF7 and BT474 cells in 24 h. When drug treatment was performed on cells with different concentrations, after 24 h, tetrazolium salts, the most important of which is MTT, were used to determine cell mortality. This experiment was performed on the reduction and breaking of yellow tetrazolium crystals by the enzyme succinate dehydrogenase in cells and the formation of insoluble blue crystals. Finally, with the absorption rate of 571 nm by the solution in the well, the amount of living cells active in them is shown in Chart 1.

The results of MTT test at concentrations of 0, 1, 2.5, 5 and 10 µg/mL doxorubicin after 24 h on MCF7 and BT474 cells showed that these cancer cell lines decreased their survival by increasing the concentration of doxorubicin. Therefore, in both cell lines under the influence of doxorubicin at all concentrations, the difference in survival was significant compared to the control group. Chart 2 shows both cells next to each other, indicating that MCF7 cells were more affected by doxorubicin than BT474 cells. In addition, comparison of viability changes in four different concentrations of doxorubicin between the two cells showed that in all concentrations there was a significant difference between the viability rates in the two cells, which was significant for concentrations 1 (P=0.003), 2.5 (P=0.003), 5 (P=0.00009), and 10 (P=0.0001) respectively.

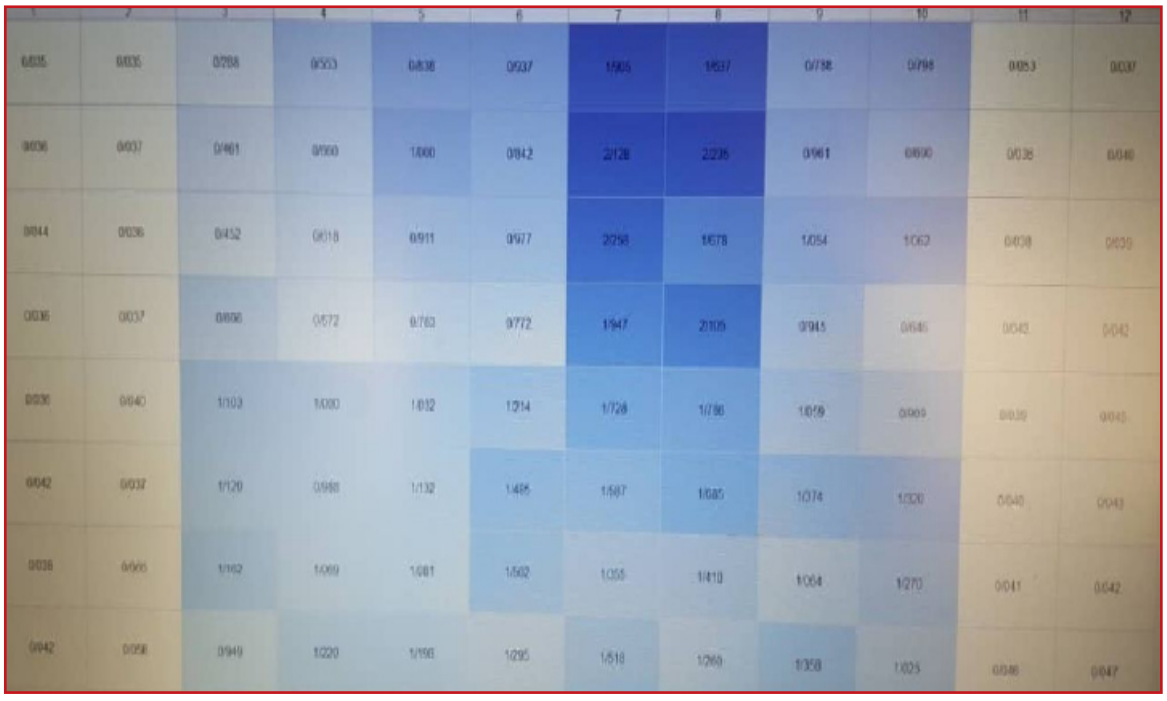

Figure 2. MTT results of two cells tested

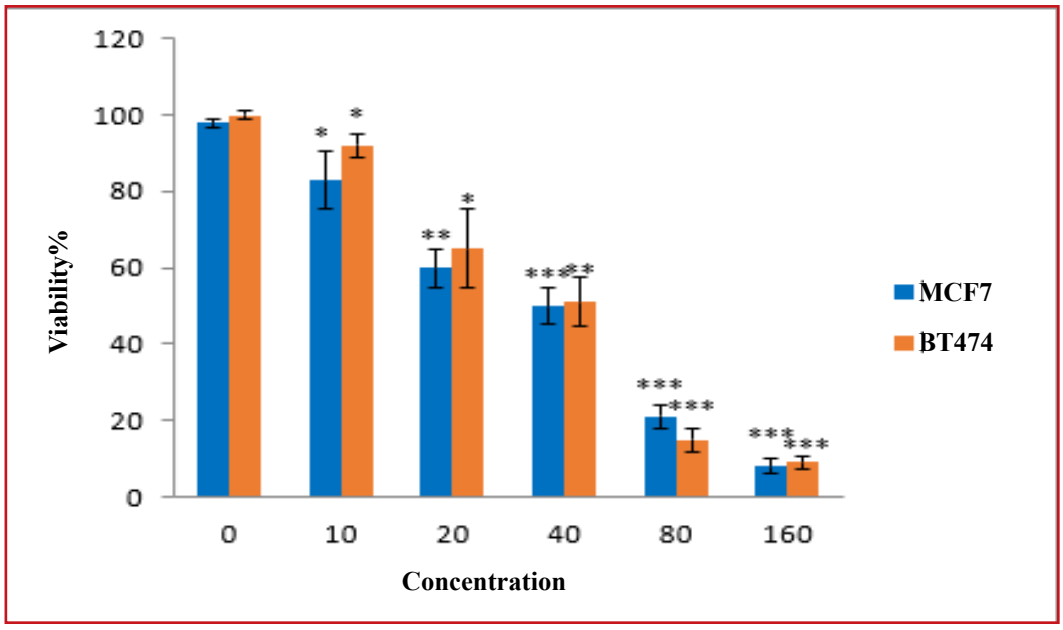

Chart 1. Comparison of survival percentage of MCF7 and BT474 cell lines under quercetin effect. Concentration in micrograms per milliliter

There is a significant difference between each group and its control group that:
* The sign indicates the significance of the comparison made at the level of $p<0.05$
** The sign indicates the significance of the comparison made at the level of $P<0.01$
*** The sign indicates the significance at the level of $p<0.001$

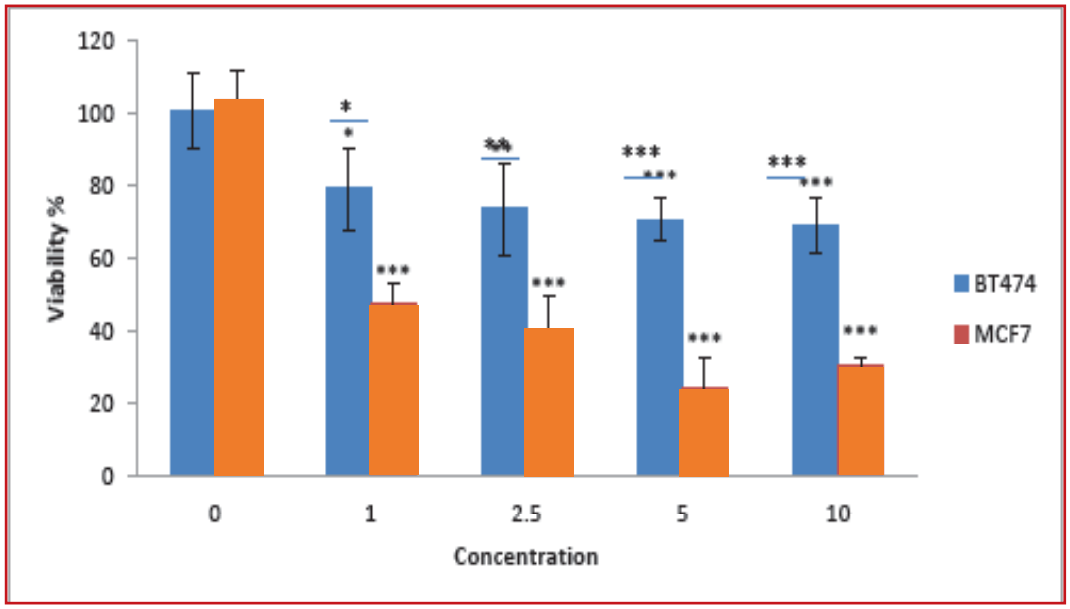

Chart 2. Comparison of the survival percentage of MCF7 and BT474 cell lines due to doxorubicin. The stock concentration of doxorubicin is 10 mg/mL

There is a significant difference between each group and its control group that:
* The sign indicates the significance of the comparison made at the level of $p<0.05$
** The sign indicates the significance of the comparison made at the level of $P<0.01$
*** The sign indicates the significance at the level of $P<0.001$

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Determination of IC50 concentration

The concentration at which 50% of cell death occurs is known as IC50. According to the results, a concentration of 40 µg/mL of quercetin was considered as IC50 quercetin on two cancer cell lines within 24 h. The stock concentration of doxorubicin was 10 mg / mL, which according to the results of the MTT test within 24 h for MCF7 cancer cell line was approximately 1 µLof stock 10 mg/mL doxorubicin, which resulted in 50% survival that is equal to 0.1 mg/mL. For doxorubicin BT474 LC50 line cells are not reported because at high concentrations the mortality rate does not reach 50%. It should be noted that a concentration of 0.1 mg/mL was used in subsequent experiments.

Results of apoptosis using flow cytometry

Flow cytometry was used to evaluate the extent of apoptosis in MCF7 and BT474 cancer cell lines as a result of incubation with quercetin and doxorubicin (QU-DOX) compared to the control and DOX groups shown in chart 3. IC50 concentrations of quercetin and doxorubicin were used for flow cytometry to determine the extent of apoptosis. The results of Annexin and PI (Propidium iodide) test showed an increase in apoptosis in MCF7 breast cancer cell lines compared to the control group and caused a significant increase in apoptosis compared to the control group. The result was similar to BT474 cells, indicating that the doxorubicin-quercetin mixture increased apoptosis in the BT474 cancer cell line compared to the control group, and with the BT474 cell line the percentage of apoptotic cells increased significantly compared to the control group.

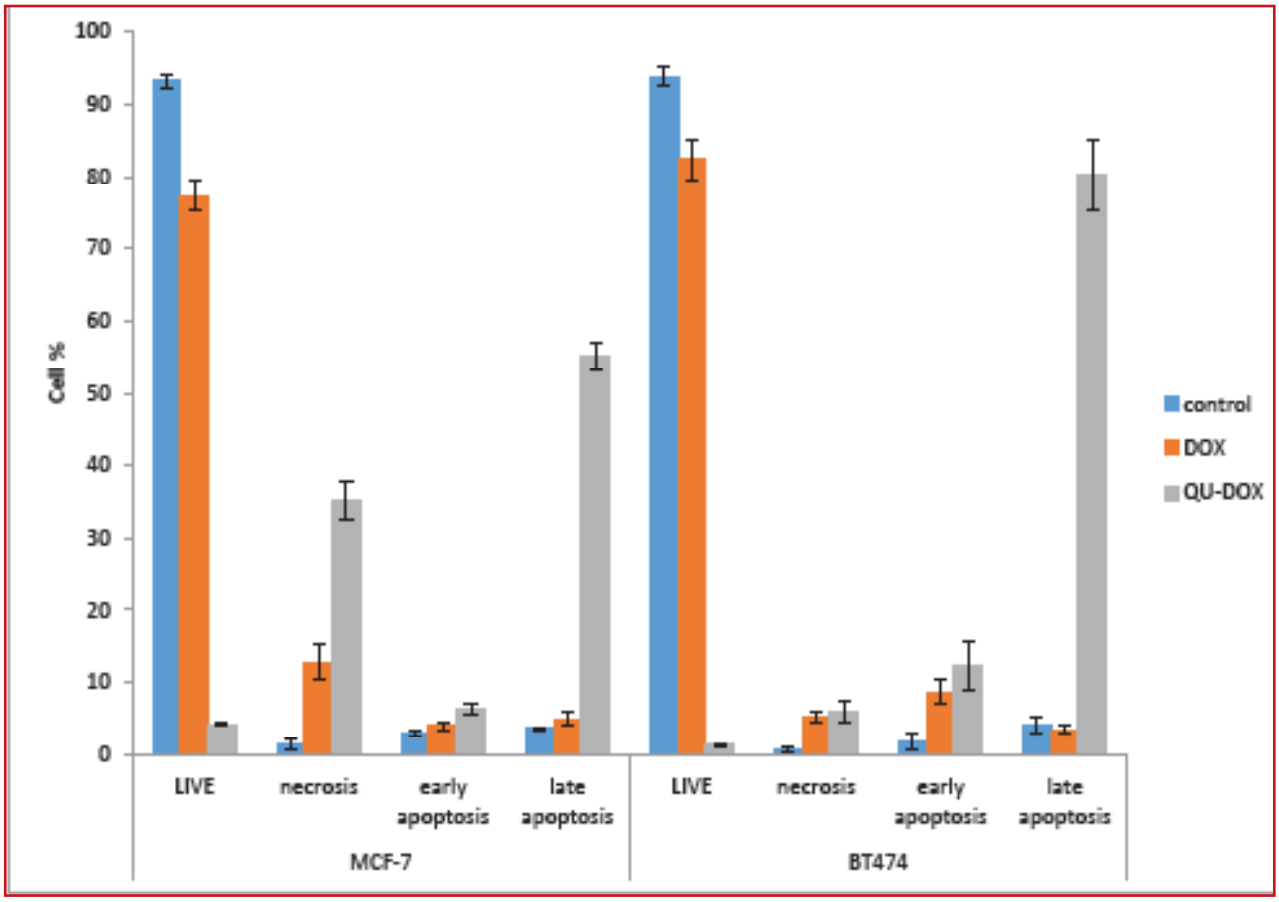

Chart 3. Comparison of apoptosis rates between cancer line cells studied (P<0.001)

According to the results of graphs related to the two cell lines, a significant increase in apoptosis in both cell lines occurred after incubation with quercetin and then incubation with doxorubicin. In MCF-7 cells, the rate of cell-to-cell mortality necrotic cells were also present, while in BT474 cells most mortality was related to the process of cell apoptosis. Dual t-test analysis between Q-DOX group and the other two groups, namely DOX and control for both cell lines, showed a significant final apoptosis in the Q-DOX group compared to the other two groups. In MCF-7 cells, the rate of necrosis was also significant compared to the other two groups.

Discussion

In this study, the effect of quercetin and its concomitant use with doxorubicin on MCF7 and BT474 breast cancer cell lines were studied. The results of the MTT test showed that the cytotoxic effects of quercetin were dose-dependent, so that increasing the quercetin concentration reduced the survival of both cell lines.

The results of this test also showed that BT474 cells are resistant to doxorubicin and have higher survival than MCF7 cells. While in the apoptosis test, the results only indicate that the presence of quercetin-doxorubicin shows its inhibitory effect mostly on the cells. Quercetin showed higher results at higher concentrations. Experiments also showed that co-administration of quercetin and doxorubicin was greater than that of quercetin alone, and that doxorubicin could be considered as a complement to quercetin-sensitive. A similar study in recent studies on the combination of graphene oxide and Doxorubicin on breast cancer cell lines showed that the combination of these two substances was more effective in killing cancer cells (15). Cancer is one of the most important problems today. It is health and wellness. The number of patients with this disease in Iran and the world is increasing year by year. Hence, many researchers are researching it. A study on leukemia by Shuo Liu (2020) showed that by increasing the intracellular accumulation of doxorubicin and facilitating doxorubicin-induced apoptosis, the cytotoxicity of doxorubicin on leukemia cells (MDA-MB-231/MDR1) increased. Possible reverse mechanisms of MDR are that pretreated cells loaded with quercetin mixed micelles reduce p-glycoprotein expression to reduce doxorubicin flow, as well as mitochondrial-dependent apoptotic pathways to accelerate DOX-induced apoptosis (16). In addition, this combination strategy can not only enhance tumor targeting efficiency in vivo, but also increase the antitumor effect in nude mice with MDA-MB-231/MDR1 without toxicity or side effects. These studies have shown that concomitant administration of natural compounds and chemotherapy drugs can be an effective strategy to overcome tumor MDR (17). Another study by Ezzati et al. on the effect of quercetin in stopping the growth of breast tumors showed that quercetin due to its vital properties such as anti-inflammatory, antioxidant and even its effect on proliferation, angiogenesis or apoptosis as an anti-tumor substance was considered to improve the treatment of breast cancer (9). Another study by Niazvand et al. In 2019 on cytotoxicity showed that QT-SLN inhibited the growth of MCF-7 cells with low IC50 (50% inhibitory concentration) compared to free QT. QT-SLN significantly reduced the survival and proliferation of MCF-7 cells, compared with QT alone. The use of QT-SLN also significantly reduced Bcl-2 protein expression, while Bx expression showed a significant increase compared to QT-treated cells. In addition, QT-SLNs significantly increased the rates of apoptosis and necrosis in MCF-7 cells. According to this study, SLN significantly increased the toxic effect of QT against human breast cancer cells (18). It showed the potential of anti-cancer effect in vitro and in vivo of quercetin-loaded polymer nanoparticles compared to pure quercetin (19). Another study by Yang Zhou (2020) on triple-negative breast cancer (TNBC), a type of breast cancer that demonstrates highly invasive tumor biology, found that quercetin is a plant flavonoid in many plants. UPA inhibits low bioavailability

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and moderate drug efficacy. However, nanoparticles-quercetin (Qu-NPs) have a uniform spherical morphology with an average diameter of 198.4 ± 7.8 nm and a suitable drug loading capacity (8.1 4 4.4). In addition, quercetin-nanoparticles (Qu-NPs) (significant) inhibition of growth and metastasis in TNBC cells showed that following oral gavage, a significant antitumor effect of Qu-NPs on mice with 4T1 with a tumor inhibition ratio of 67.88% and fewer metastatic lung colonies were observed. In addition, the inhibitory effect of quercetin on uPA knockdown migration of MDA-MB231 cells was greatly attenuated. Mixing Qu-NPs with uPA inhibition significantly improved the antitumor and anti-metastatic effects which provided a new strategy for the treatment of TNBC (20). Hui Sun and colleagues also showed that quercetin has high immunosuppressive and inhibitory effects on various cancers, but its low bioavailability limits its clinical application. To overcome this defect, quercetin bioavailability has been improved by chemical modification and composite carrier. In this study, they showed that nanoquercetin carriers increased quercetin in the treatment of breast cancer (21). Li Lv et al., while studying MCF7 breast cancer cells, showed that the biotin receptors quercetin and doxorubicin target nanoparticles to minimize drug resistance in breast cancer (22). In experiments on lung diseases, Liu et al. showed that the loading of paclitaxel and quercetin nanoparticles into the microspheres caused the lung drug to last longer. Another study found that co-administration of quercetin and doxorubicin with mesoporous silica nanoparticles increased the effect of chemotherapy on gastric carcinoma (23, 24).

Conclusion

The results show that in both cell lines, an increase in apoptosis in both cell lines occurred after incubation with quercetin and then incubation with doxorubicin. While in BT474 cells most mortality is related to the process of cellular apoptosis. Also, comparison of doxorubicin, Quercetin and Quercetin and doxorubicin groups with control shows that with the presence of quercetin, doxorubicin has a greater inhibitory effect on cells.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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