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Portulaca oleracea Protects H9c2 Cardiomyocytes Against Doxorubicin-Induced Toxicity by Inhibition of Oxidative Stress and Apoptosis

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ABSTRACT

Background & Objective: Doxorubicin as an effective chemotherapeutic agent is frequently used in various cancers. Nowadays, the application of doxorubicin is limited due to its cardiotoxic effects. The important mechanism which is involved in the cardiac injury of doxorubicin is the generation of reactive oxygen species; therefore antioxidant compounds may reduce cardiotoxicity. In the present study, we evaluated the protective effects of *Portulaca oleracea* extract against doxorubicin-induced damage in cardiomyocytes cell line H9c2.

Materials & Methods: The H9c2 cells were pre-treated for 2h with different concentrations of extract (12-400µg/ml) or resveratrol (50µM, positive control), and then doxorubicin was added for 24h. Afterward, the cell viability, and parameters of oxidative stress including lipid peroxidation and reactive oxygen species (ROS) generation, and also apoptosis rate, were measured.

Results: The results revealed that doxorubicin extremely decreased cell viability via increasing malondialdehyde, ROS, and apoptotic cells. The extract could reverse doxorubicin-induced cardiotoxicity through anti-oxidant activity.

Conclusion: In conclusion, we witnessed that *P. oleracea* has protective effect against doxorubicin-caused cardiomyocytes damage.

Keywords: Cardioprotective agents, Doxorubicin, Cardiomyocytes , *Portulaca oleracea*

Introduction

Doxorubicin (DOX), is a member of the anthracycline family, which is frequently used as a chemotherapeutic agent in the treatment of solid and hematologic cancers (1). Despite therapeutic utilization, the clinical administration of DOX is limited due to its adverse effects, especially cardiotoxicity; change in the function, or structure of cardiomyocytes (2, 3). Different mechanisms play role in DOX-induced cardiotoxicity, however, the production of reactive oxygen species (ROS) is more important. Increasing free radicals leads to lipid peroxidation, reduction of anti-oxidant enzymes, and apoptosis (4). Nevertheless, anti-oxidant compounds may decrease doxorubicin toxicity via the scavenging of free radicals. The studies have reported that dexrazoxane decrease DOX-induced cardiotoxicity but attenuates the chemotherapeutic effects of DOX (5, 6). Today, medicinal herbs are applied in different diseases as supplementary or replacement for chemical drugs due to their various properties and their active ingredients (7). *In vivo* and *in vitro* studies have shown some medicinal herbs or active ingredients reduce DOX toxicity (8, 9). In in vitro models, the H9c2 cell line is considered as an appropriate *in vitro* model for studying DOX-induced cardiotoxicity because of its ability to differentiate into skeletal or cardiac muscle phenotypes (8).

Portulaca oleracea (*P. oleracea*) belongs to the Portulacaceae family which has various names in different regions such as qurfeh (Persia), purslane (the USA and Australia), pigweed (England), rigla (Egypt), pourpier (France), and Ma-Chi-Xian (China) (10). It grows in tropical Asian countries, the United States, and the Mediterranean (10). In folk medicine, *P. oleracea* is used for febrifuge, antiseptic, and anthelmintic properties (11). Other pharmacological properties are including muscle relaxant activity (12), decreasing locomotor activity (13), anti-convulsant (14), anti-oxidant (15), and anti-inflammatory (16). The anti-oxidant activity of *P. oleracea* is related to the presence of compounds such as gallotannins, omega-3 fatty acids, ascorbic acid, α-tocopherols, kaempferol, quercetin, and apigenin (17, 18). Various studies have reported cardioprotective effects of the active ingredient of *P. oleracea* such as quercetin (19, 20), α-linoleic acid (21), kaempferol (22), and apigenin (23, 24) against doxorubicin. In this research, we evaluated the protective effect of the methanolic extract of *P. oleracea* against DOX-induced toxicity in H9c2 cells. Resveratrol as a phenol compound is found in plants such as grapes, peanuts, and berries. Some studies have shown cardioprotective effects of resveratrol against doxorubicin toxicity (25, 26).

In the current study, we demonstrated that *P. oleracea* extract significantly decreased DOX-induced cardiomyocyte death, which depended on its ability to attenuate oxidative stress and apoptosis.

Materials and Methods

Reagents

The H9c2 cell line was obtained from the Pasteur Institute, Tehran, Iran. Glucose-high Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), and penicillin-streptomycin were purchased from Gibco (Grand Island, NY). Dimethyl sulfoxide (DMSO) was purchased from Merck (Darmstadt, Germany). Propidium iodide (PI), sodium citrate, Triton X-100, Dulbecco's Phosphate-buffered saline (PBS), resveratrol, dichlorodihydrofluorescein diacetate (H2DCF-DA), doxorubicin (DOX), and 4,5-Dimethylthiazol-2-yl,2,5-diphenyl tetrazolium (MTT) were obtained from Sigma (St Louis, MO, USA). The study was approved by the Animal Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1397.070).

Preparation of the extract

The plant material was powdered by a blender. To prepare the methanolic extract of *P. oleracea*, 50 g of the powder was percolated with 95% methanol at room temperature for 24. The solvent was removed using a rotary evaporator and the extract was dissolved in DMSO and stored at -20°C (27).

Cell culture and treatment

The H9c2 cells were maintained in high glucose DMEM with 10% FBS, and 1% of antibiotics (penicillin-streptomycin, 100 U/ml) at 37 °C in a 5% CO_2 atmosphere. After achieving about 70–80% confluency, the cells were seeded (10^4 cells per well) in 96-well plates for measuring viability, and 10^6 cells/well in 6-well plates for other tests. Then, the monolayer cells were incubated with the fresh media containing *P. oleracea* extract (12-400 µg/ml) or resveratrol (50 µM) for 2h before exposure to DOX (5 Mm) for 24h.

Determination of cell survival by MTT assay

After the treatments, MTT solution (10 µl) was added to each well (final concentration of 0.5 mg/ml). After a 3h incubation at 37°C, the supernatant was discarded and the formazan crystals were dissolved by DMSO (100 µl). The absorbance was measured at 490 and 650 nm using a microplate reader. The absorbance of each group was normalized to that of the control group (28).

Measurement of ROS generation

To detect intracellular ROS level in the treated cells, 10 µl of dye 2′,7′dichlorodihydrofluorescein diacetate (10 µM, DCFH-DA) was added to each well. After incubation in dark for 30 min at 37°C, the flouresence intensity was recorded by fluorescence multi-well plate reader (excitation/emission: 485 nm and 530 nm) (29).

Determination of lipid peroxidation

The lipid peroxidation level was measured by calculating the concentration of malondialdehyde (MDA), which is the key product of lipid peroxidation and reacts with TBA to generate fluorescence adduct following the method of previous studies (30). At the end of the incubation time of the cultured cell with *P. oleracea* extract, resveratrol, and DOX, a homogenate of cell lysate in trichloroacetic solution (1 ml, 2.5%) was prepared. The supernatant of the samples was separated and then thiobarbituric acid (0.67% w/v, 0.8 ml) and trichloroacetic acid (15% w/v, 0.4 ml) were added. Thereafter, the tubes were placed in boiling water. The mixture was cooled and the absorbance of the upper solution was then read using spectroflourimeter at 532 nm. The data were presented as percentages of the control (untreated group).

Flow cytometry detection of apoptotic cell death

Briefly, DNA staining was performed with PI (5 mg/100 ml, 30 min) in the cells treated with or without *P. oleracea* extract or resveratrol. Flow cytometer (FACS Calibur flow cytometer; BD Biosciences, USA) measured the cell cycle in each sample (A minimum of 10,000 cells). Finally, DNA histograms were analyzed using Flow Jo 7.6.1 software (31).

Statistical analyses

Comparisons between groups were carried out using one-way ANOVA analysis and Tukey, respectively. The data were statistically analyzed using Prism 8 and reported as mean ± SEM or percentage. P value less than 0.05 statistically indicated significance.

Results

Effect of *P. oleracea* on H9c2 cell viability

The H9c2 cells were incubated with increasing concentrations of *P. oleracea* extract for 24h. The findings showed that the extract at the concentration range of (12-400 µg/ml) did not have cytotoxic effect on cells, as compared with the control group ($p > 0.05$, Figure1).

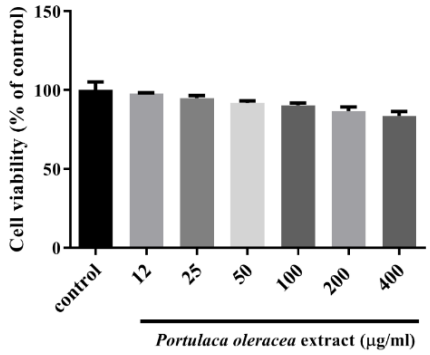

Figure 1

Figure 1. Effect of *P. oleracea* on H9c2 cell viability. Cells were incubated with different concentrations of extract for 24 h. Cell viability was determined by MTT assay. Data are mean±SEM of three separate experiments.

Protective effect of *P. oleracea* against doxorubicin-induced toxicity in H9c2 cell

In this experiment, DOX exposure with a concentration of 5 µM for 24h could significantly reduce cell viability ($p<0.001$). Cells pre-treatment with extract at 12-400 µg/ml concentrations for 2h could attenuate DOX toxicity at concentration of 50, 100 and 200 µg/ml ($p<0.01$, $p<0.001$, $p<0.001$, respectively). Also, resveratrol with a concentration of 50 µM decreased DOX-induced toxicity ($p<0.001$, Figure 2).

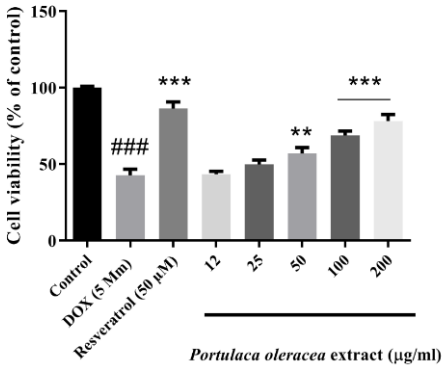

Figure 2

Figure 2. Effect of *P. oleracea* and resveratrol on doxorubicin-induced toxicity in H9c2 cell. The cells were pretreated (for 2 h) with different concentrations of extract and resveratrol before to exposure to doxorubicin. Data are expressed as mean ± SEM of three separate experiments. ### p<0.001 vs control, ** p<0.001 and *** p<0.001 versus doxorubicin.

The *P. oleracea* extract decreased doxorubicin-induced ROS production in H9c2 cell

Results showed that DOX significantly increased the generation of ROS compared to the control group (283 ± 1.68% *vs* 100 ± 1.5 %, $p<0.001$). The cells were pre-treated with extract for 2h and then doxorubicin was added. After 24h, *P. oleracea* extract concentrations of 50, 100, and 200 µg/ml attenuated ROS production following DOX-induced toxicity ($p<0.01$, $p<0.001$, $p<0.001$, respectively, Figure3). Moreover, resveratrol 50 µM decreased DOX-induced toxicity ($p<0.001$).

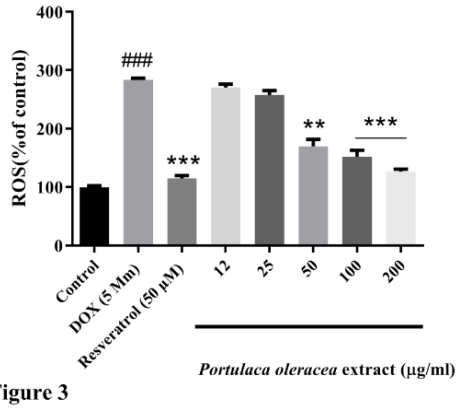

Figure 3

Figure 3. Effect of *P. oleracea* and resveratrol on doxorubicin-induced reactive oxygen species (ROS) generation in H9c2 cells. The cells were pretreated (for 2 h) with different concentrations of extract and resveratrol before to exposure to doxorubicin. Data are expressed as mean ± SEM of three separate experiments. ### p<0.001 vs control, ** p<0.001 and *** p<0.001 versus doxorubicin.

The *P. oleracea* extract decreased doxorubicin-induced MDA production in H9c2 cell

Increasing ROS production leads to lipid peroxidation and elevation of MDA. As shown in Figure4, DOX significantly increased the amount of MDA in comparison with the control group ($p<0.001$), while pre-treatment cells with extract reduced the level of MDA at 50, 100, and 200 µg/ml concentrations. (respectively: $p<0.01$, $p<0.01$, $p<0.001$) (Figure.4). Also MDA level reduction was observed by resveratrol (50 µM, $p<0.001$).

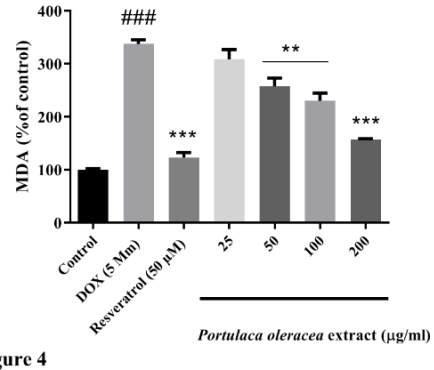

Figure 4

Figure 4. Effect of *P. oleracea* and resveratrol on doxorubicin-induced MDA production in H9c2 cells. The cells were pretreated (for 2 h) with different concentrations of extract and resveratrol before to exposure to doxorubicin. Data are expressed as mean ± SEM of three separate experiments. ### p<0.001 vs control, ** p<0.001 and *** p<0.001 versus doxorubicin.

The *P. oleracea* extract attenuated doxorubicin-induced apoptosis in H9c2 cell

As shown in Figure 5, DOX increased apoptotic cells while the *P. oleracea* extract and resveratrol treatment could suppress apoptotic cells following DOX toxicity. (7.5% in control cells *vs.* 52.2% in DOX-treated cells, and in resveratrol group 12.4%). However, when H9c2 cells were pre-treated with extract (50, 100, and 200 µg/ml), the apoptosis rate was reduced to 41%, 35% and 21%, respectively compared to DOX-injured cells.

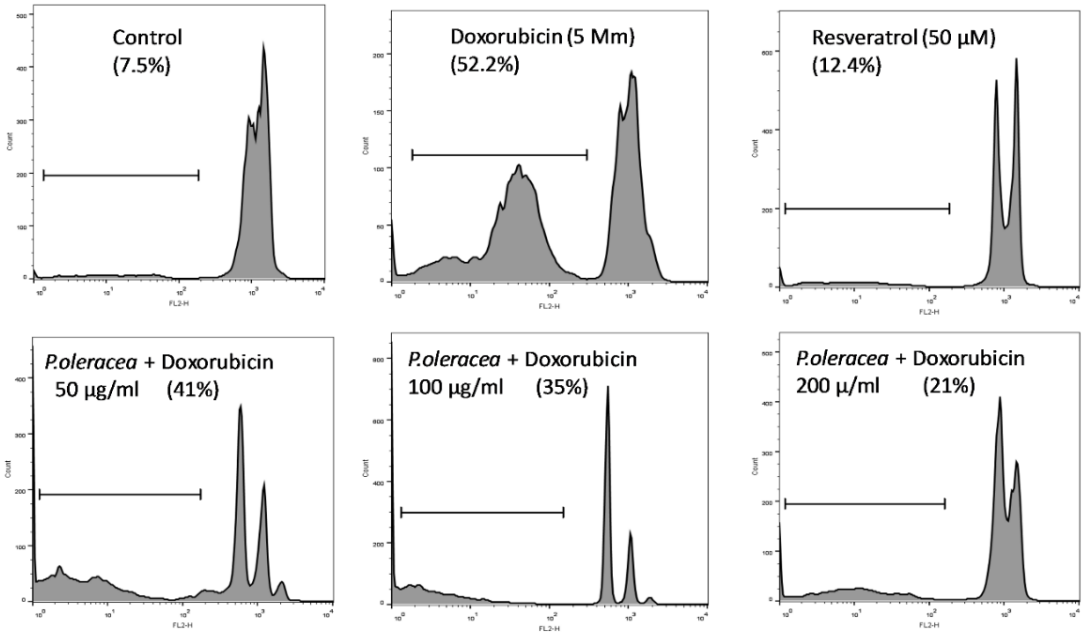

Figure 5

Figure 5. Effect of *P. oleracea* and resveratrol on the percent of H9c2 cells in sub-G1 stage.

Discussion

In the present study, we evaluated the protective effect of *P. oleracea* and resveratrol against DOX-induced cardiotoxicity in H9c2 cells. Our findings showed that DOX-induced cell death and apoptosis, and also increased the production of ROS and MDA. Moreover, we showed that *P. oleracea* extract at the concentration range of 50-200 µg/ml, effectively reduced DOX-caused toxicity via attenuation of intracellular free radicals, lipid peroxidation, and apoptotic cells which were similar to resveratrol.

DOX, as a chemotherapy drug, is applied in the treatment of different cancers including lung, breast, bladder, and leukemia (1). This drug led to acute adverse effects such as arrhythmia and chronic effects like cardiomyopathy (32). The studies have revealed that DOX causes cardiotoxicity via induction of apoptosis, generation of free radicals, and depletion of antioxidant enzymes (33). However, anti-oxidant compounds may reduce DOX-induced cardiotoxicity (34).

Nowadays, phytotherapy is considered as supplementary or alternative drug for the treatment of diseases such as cancer, Alzheimer and cardiovascular because they are composed of various active ingredients (35). *P. oleracea* is composed of various ingredients such as acid ascorbic, kaempferol, quercetin, apigenin, and β-carotene (36). The *in vitro* or *in vivo* studies have revealed quercetin, kaempferol, and apigenin decreased doxorubicin-induced cardiotoxicity. Kaempferol reduced doxorubicin toxicity in H9c2 cells via inhibition of p53 signaling and ERK-dependent MAPK pathways (22). Quercetin protected H9c2 cells against doxorubicin toxicity by attenuation of mitochondrial dysfunction, ROS generation, apoptosis, and DNA double-strand breaks while increasing the expression of Bcl-2 and Bmi-1 (19, 20). Also, in vivo study showed that quercetin reduced the cardiotoxicity of doxorubicin in mice by reduction of oxidative stress (20). α-Linolenic acid (ALA) reduced doxorubicin toxicity in rats by activating Keap1/Nrf2 pathway and anti-apoptosis

through activating protein kinase B/extracellular signal-regulated kinase pathway (21). Researchers in the *in vivo* study showed that apigenin decreased doxorubicin toxicity in cardiac by decreasing apoptotic proteins (caspase3 and Bax), increasing anti-apoptotic protein (Bcl-2) and anti-oxidant enzyme such as SOD (21). It seems that the protective effect of *P. oleracea* extract in our study is linked to the presence of these ingredients in the herb. Qiao and coworkers examined that *P. oleracea* has protective effect against acute alcoholic liver injury in rats by decreasing of MDA level and elevation of anti-oxidant enzymes (37). Also, *P. oleracea* could attenuate rotenone-induced neurotoxicity (38). The extract decreased lipid peroxidation and oxidative stress in thyrotoxic rats (39). The extract showed cardio-protective effects in hyperthyroidism rats (40). Resveratrol as positive control which is found in various medicinal herbs has anti-oxidant activity and attenuated DOX-induced cardiotoxicity *in vivo* and *in vitro* studies (25). Interestingly, the supportive effect of *P. oleracea* extract was similar to resveratrol and may be a good choice in the reduction of DOX toxicity.

Conclusion

The study has shown that *P. oleracea* extract decreased the cardiotoxicity of DOX in H9c2 cells via decreasing oxidative stress and apoptosis. More investigation is needed to perceive the accuracy of mechanisms.

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Conflict of Interest

The Authors declare no conflicts of interests.

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