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Reversal effect of quercetin on talazoparib resistance in *BRCA1* mutant triple negative breast cancer

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ABSTRACT

Objectives: Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated an outstanding activity in patients with *BRCA*-mutated and wild-type breast cancer. However, the identification of resistance mechanisms to PARP inhibitors is a significant clinical challenge in effective treatment. Thus, new therapeutic strategies are urgently needed to overcome resistance. The aim of the current study was to explore the potential effect of quercetin on HCC1937 (*BRCA1* mutant) and talazoparib (BMN 673), a PARP inhibitor, resistant HCC1937 (HCC1937-R) triple negative breast cancer cells (TNBC).

Methods: We firstly generated BMN 673 resistance HCC1937 cells by continuous exposure to BMN 673 during 6 months. Then, cells were exposed to the different concentration (0-100 µM) of quercetin and the cytotoxic and apoptotic effects of quercetin on these cells were evaluated by WST-1, Annexin V and dual acridine orange-ethidiumbromide (Et-BR) staining.

Results: The cell viability of HCC1937 and HCC1937-R cells reduced to 37.1% and 44.2% at a concentration of 100 µM, respectively for 48 h ($p < 0.01$). Apoptotic rates of HCC1937 and HCC1937-R cells treated with 100 µM quercetin were nearly 56.0% and 46.0%, respectively ($p < 0.01$). Additionally, theapoptotic morphologicalchanges were observed in these cells.

Conclusions: In conclusion, the obtained results suggest that quercetin could potentially be used as an alternative therapeutic strategy in *BRCA1* mutant TNBC to overcome acquired BMN 673-resistance.

Keywords: Triple negative breast cancer, PARP inhibitors, talazoparib (BMN 673), quercetin, apoptosis, *BRCA1*

Poly (ADP-ribose) polymerase (PARP) inhibitors have shown promising clinical activity in patients with *BRCA*-mutated and wild-type breast and ovarian cancer. Several PARP inhibitors [iniparib, talozoparib, veliparib, rucaparib and niraparib] currently being investigated in late stage (phase II-III) clinical trials and olaparib is currently approved by FDA for the treatment of *BRCA*-mutated breast cancer patients with a deficient homologous recombination (HR) pathway through synthetic lethality [1-6]. However, recognizing the role of resistance mechanisms (altered HR and nonhomologous recombination (NHEJ) capacity, changes in PARP1 activity, multiple drug resistance (MDR) and epigenetic changes) to PARP inhibitors is a major clinical challenge in successful treatment [7-9].

BMN 673 (Talozoparib) is a novel and the most potent PARP inhibitorin phase II/III clinical trials for

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BRCA1/2 mutation-associated advanced breast cancersdue to the potency in PARP-trapping[10-13]. However, some studies have revealed that acquired resistance to BMN 673 is limiting the success of future treatment options [14-16]. Thus, novel approaches are required to restore sensitivity to BMN 673.

Quercetin is a polyphenolic flavonoidwidely found in many fruits (apple, blueberries, broccoli, grape, leek), vegetables, nuts, and red wine. Quercetin exerts anti-inflammatory, anti-diabetic, anti-allergic, antiviral, anti-fungal and significant anti-carcinogenic activities. It has been reported that quercetin has a potential anticancer effect in different cancer cell lines (breast, prostate, osteosarcoma, colon, gastric, esophageal, ovarian cancer and hepatocellular carcinoma) through the induction of apoptosisboth *in vitro* and *in vivo* [17-25]. However, limited studies have shown the reversal effect of quercetin in resistance-cancer cells [26-30].

Here, for the first time, we investigated the reversal effect of quercetin on BMN 673 resistance. This study assessed the cytotoxic and apoptotic effects of quercetin on HCC1937 (*BRCA1* mutant), BMN 673-resistant HCC1937 (HCC1937-R) triple negative breast cancer (TNBC) and MCF-10A human mammary epithelial cell lines.

METHODS

HCC1937 and MCF-10A were purchased from ATCC (Manassas, VA, USA). HCC1937 and HCC1937-R cells were cultured in 5% CO2 at 37°C in RPMI medium supplemented with 10% fetal bovine serum (FBS) and 100 U/ml penicillin and 10 mg/ml streptomycin. HCC1937-R cells were generated by continuous exposure to 0.01 nM BMN 673 during 6 months. MCF-10A cells were grown in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) medium supplemented with 100 mg/ml EGF, 1 mg/ml hydrocortisone, 10 mg/ml insulin, 10% FBS, penicillin and streptomycin (100 units/ml) at 37° in a humidified atmosphere.

WST-1 Assay

HCC1937, HCC1937-R and MCF-10A cells were seeded at a density of 2x104 cells per well in 96-well plates. After overnight incubationat 37°C, the cells were treated with different concentration of quercetin for 24 and 48 hours. At the end of the treatments, 10 µl WST-1 dye (Biovision, USA) was added to every single well and plates were incubated for 1-3 hours at 37°C. Finally, the cell viability was measured at 450 nmwith a microplate reader (Tecan, Switzerland).

Annexin V and Dead Cell Assay

The apoptotic effect of quercetin on HCC1937 and HCC1937-R cells was determined by Annexin V and Dead Cell kit (Millipore, Germany). After treatment with different concentrations (12.5, 25, 50 and 100 µM) of quercetin for 48 h, the collected cells were rinsed with sterile phosphate-buffer saline (PBS). For each sample of cells, 100 µl MUSE Annexin V and dead cell reagent was added andsubsequently incubated for 30 min at room temperature. Finally, the cells were analyzed using a Muse Cell Analyzer

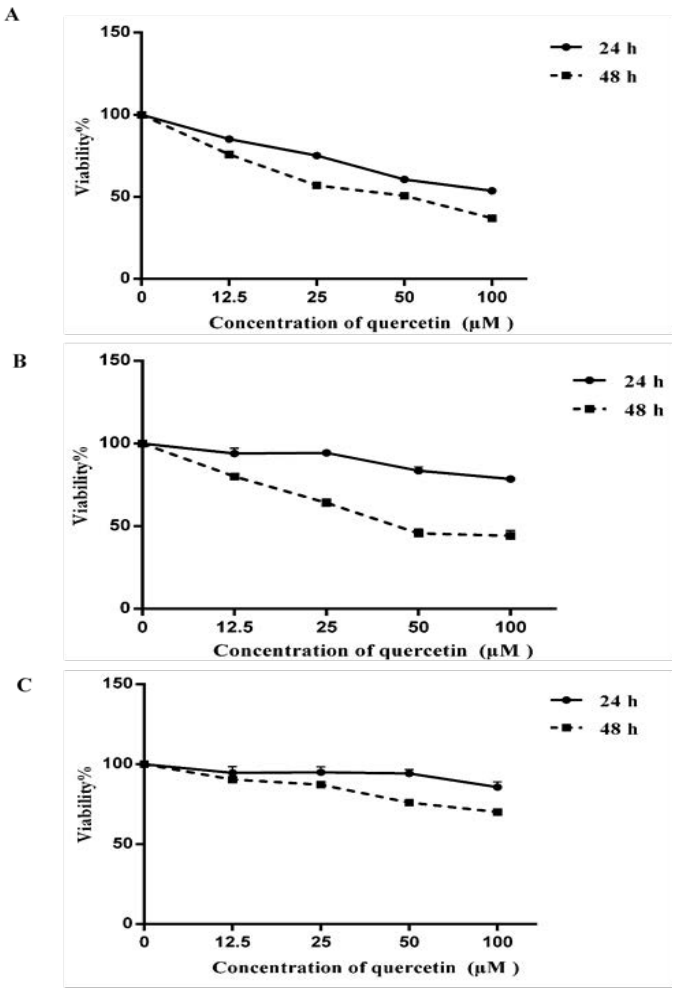

Fig. 1. The cytotoxic effects of quercetin as measured by WST-1on (A) HCC1937, (B) HCC1937-R and (C) MCF-10A cells for 24 and 48 h. Data are the means of triplicate experiments; error bars, SD ($p < 0.05$*, $p < 0.01$).**

(MuseTM EMD Millipore Co., Hayward, CA, USA).

Dual Acridine Orange (AO)/Ethidium Bromide (Et-BR) Staining

The morphological changes in quercetin-treated HCC1937 and HCC1937-R cells were observed by AO/Et-BR double staining. A total of 5×105 HCC1937 and HCC1937-R cells were seeded in 6 well plates and treated with 12.5, 25, 50 and 100 µMquercetin for 48 h. At the end of the treatments, the cells were fixed in 4% paraformaldehyde (Merck, Germany) for 30 min. After fixation, the cells were rinsedthree times with PBS. Subsequently, the cells were stained with AO/Et-BR solution (Sigma, USA) and observed under an EVOS FL Cell Imaging System (Thermo Fisher Scientific, USA).

Statistical Analysis

Statistical analysis was performedusing SPSSversion 22.0 (SPSS Inc, Chicago, IL, USA). All data analyzed were presented as mean value ± standard error of mean (SEM) (n = 3). A one-way analysis of variance (ANOVA) with post-hoc Tukey was used for comparison of multiple variables. p - value of < 0.05 was regarded as statistically significant (*p < 0.05, ** p < 0.01).

RESULTS

Cytotoxic Effect of Quercetin in TNBC

The cytotoxic effect of UA on HCC1937, HCC1937-R and MCF-10A cells wasassessed using

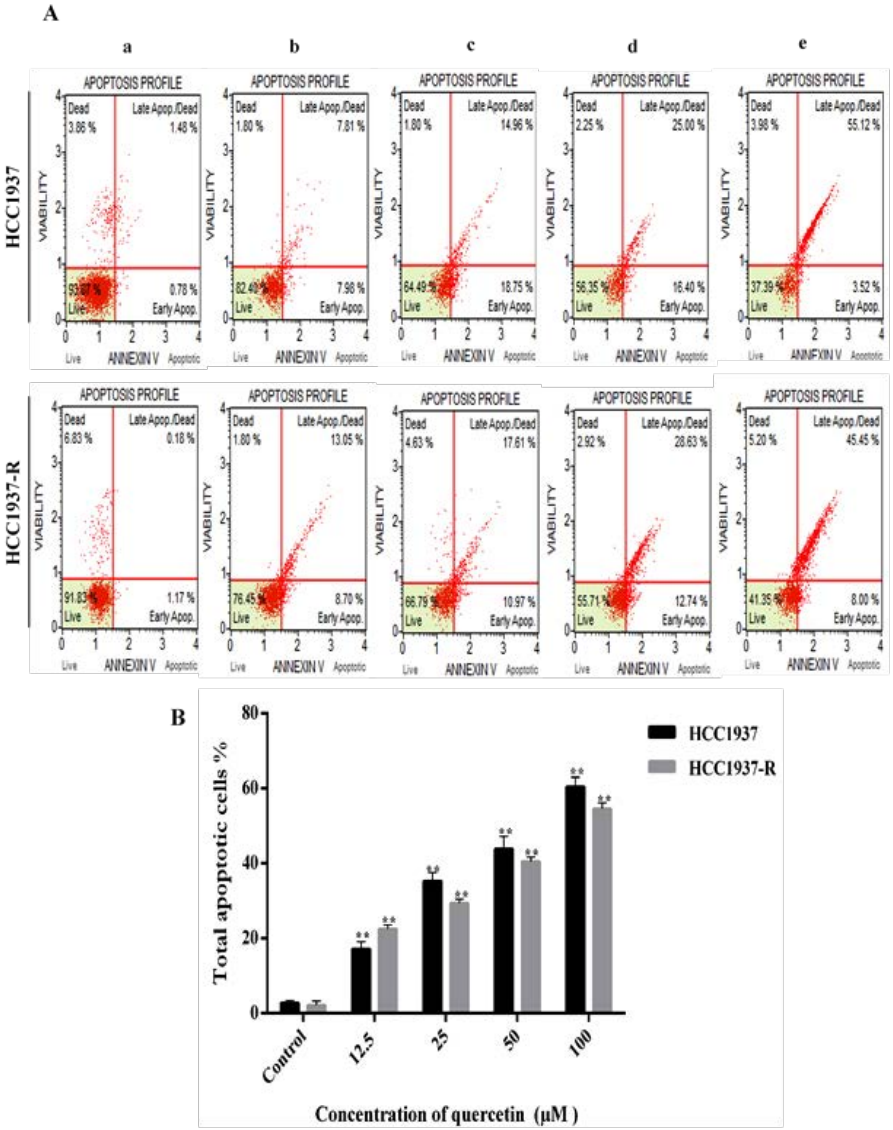

Fig. 2. The apoptotic effects of quercetin on triple negative breast cancer cells for 48 h. (A) HCC1937 and HCC1937-R cells were treated with (a) Control, (b) 12.5, (c) 25, (d) 50 and (e) 100 µM quercetin, respectively. (B) A statistical graph of total apoptotic cells after treatment with different concentration of quercetin (*p < 0.05, **p < 0.01).

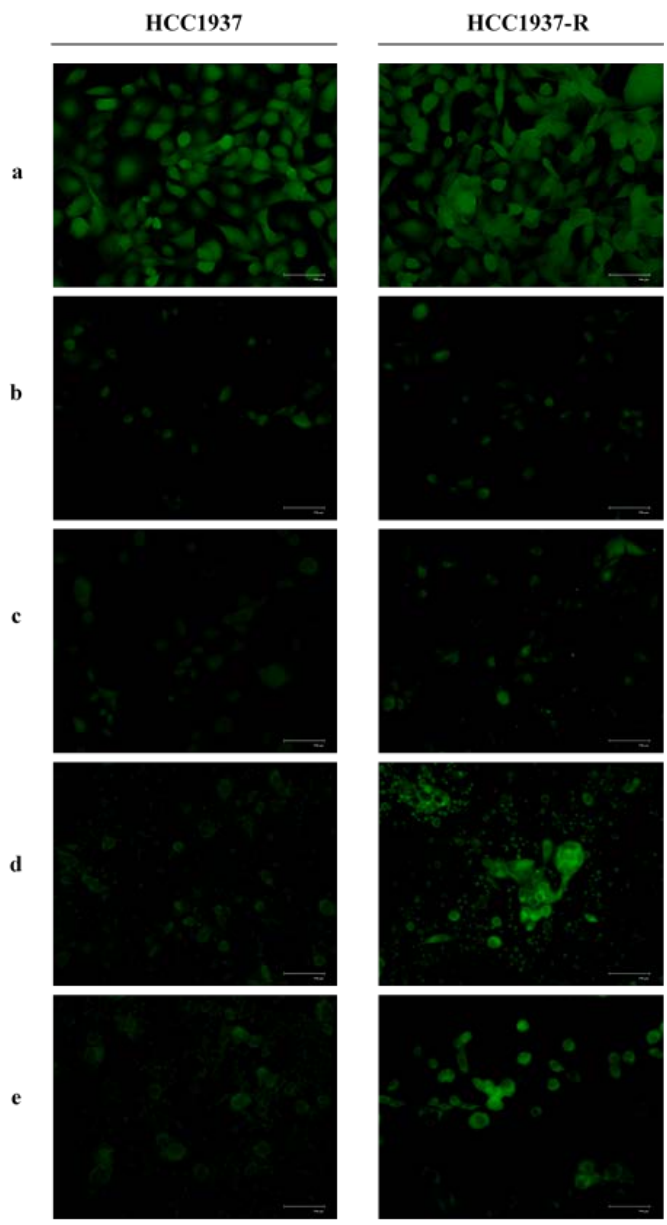

Fig. 3. AO and EtBr double-staining of HCC1937 and HCC1937-R cells following treatment with (a) Control, (b) 12.5, (c) 25, (d) 50 and (e) 100 µM quercetin, respectively for 48 h.

WST-1 assay as shown in Fig. 1. The HCC1937, HCC1937-R and MCF-10A cell viability decreased by 53.7%, 78.5% and 85.8%, respectively at concentration of 100 µM for 24 h ($p < 0.01$). After 48 h incubation, quarcetin significantly reduced the HCC1937, HCC1937-R and MCF-10A viability to 37.1%, 44.2% and 70.2%, respectively at 100 µM ($p < 0.01$). The IC50 values for quercetin in HCC1937 and HCC1937-R cells were 52.9 µM and 44.2 µM, respectively.As a result, quercetin had a considerable cytotoxic effects on HCC1937 and HCC1937-R cells and quercetin could potentially overcome BMN 673-resistance. Additionally, no toxic effects were observed with doses lower than 25 µMfor 48 h in MCF-10A cells.

Apoptotic Effect of Quercetin in TNBC

The apoptotic effect of quercetin on HCC1937 and HCC1937-R cells for 48 h was determined by Annexin V analysis and the results were summarized in Fig. 2. The percentage of late-apoptotic cells was 7.81 ± 1.9 % and 55.12 ± 2.8% at 12.5 and 100 µM of quercetin, respectively compared with control (1.48 ± 0.7%) in HCC1937 cells. Furthermore, the percentage of late-apoptotic cells increased from (0.18 ± 0.4%) to 13.05 ± 1.0% and 45.45 ± 1.7% at 12.5 and 100 µM, respectively in HCC1937-R cells. Thus, quercetin significantly induced apoptotic death in HCC1937 and HCC1937-R cells in a dose-dependent manner ($p < 0.01$).

Morphological Observations

To investigate the morphological changes in HCC1937 and HCC1937-R cells, AO/EtBr staining was performed as summarized in Fig. 3. AO/EtBr staining revealed a dose dependent apoptotic cell death in HCC1937 and HCC1937-R cells when exposed to quercetin for 48 h. Quercetin induced nuclear condensation, cellshrinkage and rounding and membrane blebbing in these cells. These findings were confirmed by WST-1 and Annexin V analysis.

DISCUSSION

In the current study, we investigated the effect of quercetin on the reversal of BMN 673-resistance in TNBC cells. Our results demonstrated that quercetin could potentially reverse BMN 673-resistance and exerted therapeutic effects on HCC1937 and HCC1937-R cells through induction of apoptosis.
PARP inhibitors have attracted attention in pre-clinic and clinic to treat particularly *BRCA1/2* mutant breast and over cancers due to inducing synthetic lethality. Three PARP inhibitors (olaparib, rucaparib, and niraparib) have now been approved by the FDA for patients with BRCA-mutated ovarian cancer [5, 31, 32]. Additionally, The FDA has also approved olaparib for patients with *BRCA*-mutated breast cancer. However, phase II/III trial of olaparib and iniparib

failed to show an improvement in disease-free survival and/or overall survival (5.7 months) and significant clinical responses in patients with TNBC [33-36]. Thus, novel PARP inhibitors including BMN 673 [13], niraparib [37], rucaparib [38] and veliparib [39,40] which exhibit synthetic lethality in patients with *BRCA1/2* mutation have gained considerable attention.

In vivo and in vitro studies of BMN 673 demonstrated excellent efficacy against breast, non-small cell lung, chronic lymphocytic leukemia (CLL), prostate, endometrial and ovarian cancer cells [10, 11, 41-44]. However, there are now several studies in the literature stating that particular resistance mechanisms could affect the clinical successes of PARP inhibitors [8, 9, 45-48]. Previous studies from our lab demonstrated that HR and multi-drug resistance (MDR) mechanisms played a major role in the development of resistance to BMN 673. Besides, we found that HCC1937-R cells was almost 3.0-fold more resistant to BMN 673 than HCC1937 parental cells [49,50]. Therefore, development of new treatment strategies to overcome resistance are important for clinical utilityof PARP inhibitors.

Quercetin, a polyphenolic compound, has been shown to induce cytotoxicity and apoptosis in different cancer cells. Quercetin induces apoptosis in cancer cell lines by the intrinsic pathway due to interaction with DNA directly [18-20, 23-25].Furthermore, it has been reported that quercetin could overcome the acquired resistance to chemotherapeutic agents (tamoxifen, 5-FU and enzalutamide) [26, 28, 30]. For this purpose, the multi-drug resistance reversal activity of quercetin was evaluated in the current study. Our results showed that quercetin remarkably decreased proliferation and induced apoptosis in HCC1937 and HCC1937-R cells. These effects were enhanced with increasing concentration and exposure time of quercetin. However, we found no significant reduction in MCF-10A cell viability evenat the lowest concentration for 48 h or short-term exposure (24 h) of quercetin.

Furthermore, previous report demonstrated that quercetin displayed PARP inhibitory effects through synthetic lethality to *BRCA2*-deficient cells and induced significantly DNA damage on V79 Chinese hamster lungwild-type cells, its *BRCA2* mutant (V-C8) and genetically complimented mutant with human *BRCA2* (V-C8 hBRCA2)[51,52]. Thus, one of the possible mechanism is quercetin can interfere with DNA and may be able to overcome BMN 673 resistance thanks to its PARP inhibitory effect. However, the underlying mechanisms towards overcoming BMN 673 resistance should be explored. The preliminary results indicated that quercetin could be a potent candidate and reverse BMN 673 resistance.

CONCLUSION

In conclusion, the present study indicated that quercetin had a potential flavonoid to reverse BMN 673 resistance by inducing apoptosis. However, quercetin-induced synthetic lethality and associated mechanisms (homologous recombination, non-homologous recombination and multi-drug resistance) in BRCA1 mutant TNBC cells should be elucidated by in vitro and in vivo experiments.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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