Dapagliflozin exerts cardioprotective and anti-inflammatory properties against Doxorubicin and Trastuzumab induced cardiotoxicity

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PURPOSE

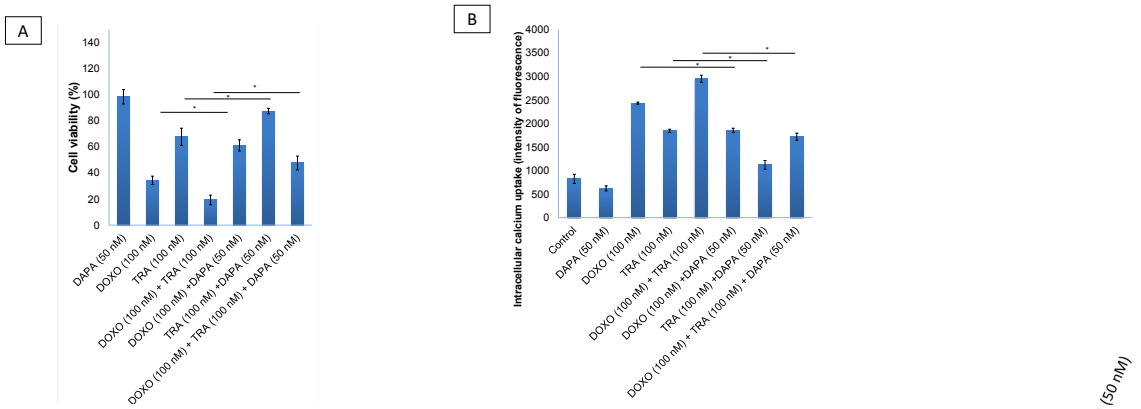
The clinical trial "DECLARE-TIMI 58" (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), demonstrated that Dapagliflozin, a Sodium glucose co-transporter 2 inhibitor (SGLT2i), reduces the composite end point of cardiovascular death/hospitalization for heart failure in a broad population of patients with type 2 diabetes mellitus. Additive cardiotoxicity induced by trastuzumab in breast patients with prior exposure to anthracyclines have significant negative implications on cancer related outcomes We aimed to study if Dapagliflozin could exerts cardioprotective and anti-inflammatory effects in Doxorubicin and Trastuzumab-induced cardiotoxicity

METHODS

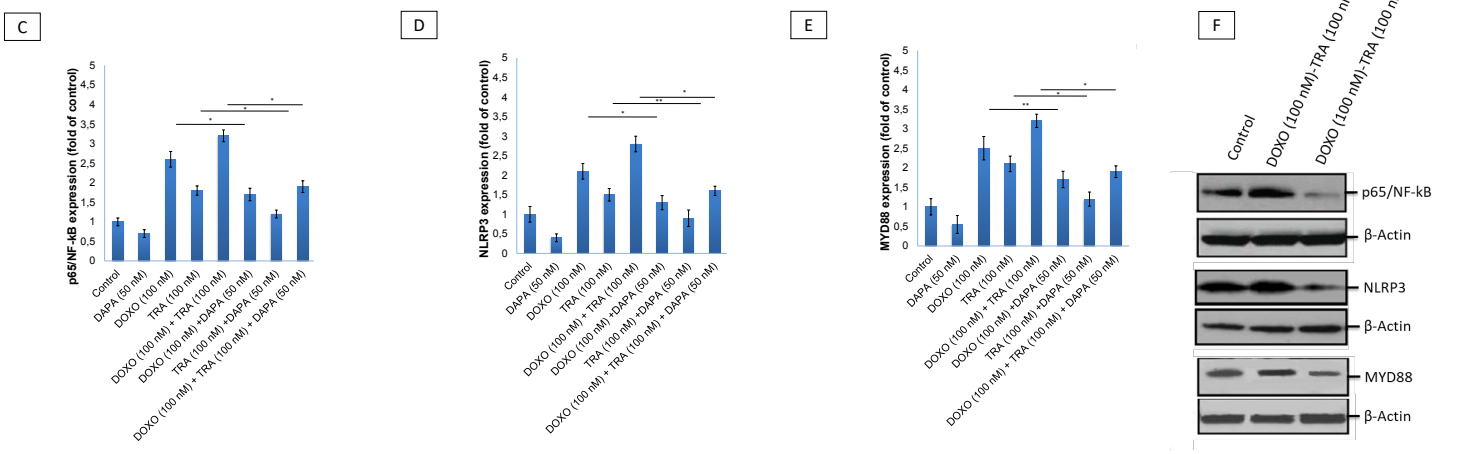
HL-1 adult cardiomyocytes were exposed to subclinical concentration of Doxorubicin and Trastuzumab (100 nM) alone or in combination with Dapagliflozin at 50 nM for 72h. After the incubation period, the following tests were performed: determination of cell viability, study of intracellular Ca2+ homeostasis. Moreover, studies on the inflammation state of cardiomyocytes were also performed (activation of NLRP3-MYD88 inflammasome; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins (IL)1β, 8 and 6). Protein expression of NLRP3, MYD88 and p65/NF-kB were also analyzed through Western blotting.

RESULTS

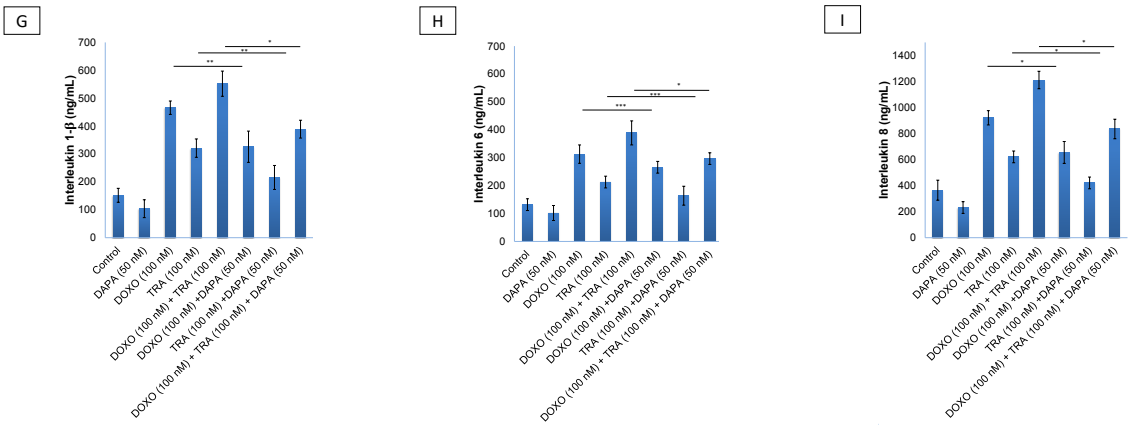
Dapagliflozin increases the viability of cardiomyocytes during exposure to Doxorubicin and Trastuzumab (A) through the reduction of intracellular Calcium overload (B) *** P<0.001 ; **P<0.01 ; *P<0.05 ; ns: not significant



Dapagliflozin inhibits the expression of NLRP3 inflammasome (C,F), MYD88 (D,F) and p65/NF-kB (E,F) in cardiomyocytes during exposure to Doxorubicin and Trastuzumab



Dapagliflozin reduces the cardiac expression of Interleukin 1-β (G), 6 (H) and 8 (I) during exposure to Doxorubicin and Trastuzumab *** P<0.001 ; **P<0.01 ; *P<0.05 ; ns: not significant



CONCLUSIONS

Dapagliflozin demonstrated cardioprotective properties during Doxorubicin and Trastuzumab exposure. Dapagliflozin improves the Ca^{2+} homeostasis and inhibits the pro-inflammatory "NLRP3- NF-κB –cytokines" pathways in cardiac cells. This preliminary research turns the light on the cardioprotective properties of Dapagliflozin in HER2+ breast cancer patients.

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The authors declare no conflicts of interest