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Venetoclax Induces Cardiac Damage through Modulation of Oxidative Stress-Mediated Cardiac Inflammation and Apoptosis via NfkB and BCL-2 Pathway

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INTRODUCTION

Venetoclax (VTX) or (ABT-199) is a promising novel agent that has been proven to have high efficacy in multiple hematological diseases, especially acute myeloid leukemia (AML)and chronic lymphocytic leukemia (CLL) with 17p deletion. However, spectrum of side effects has been reported with VTX treatment, including tachycardia, cardiomyopathy, and other health related problems. Considering its mechanism of action, which is inhibition of BCL-2 protein by targeting the BH3 domain of BCL-2, the possibility that VTX may cause cardiotoxicity cannot be ruled out. Therefore, in the current study we focused on investigating the effect of BCL-2 inhibition on the heart function and whether VTX can result in cardiotoxicity. To the best of our knowledge, there is no such preclinical report or data available which has shown the toxic effects of VTX on vital organs, such as heart, liver and kidney.

OBJECTIVES

Hypothesis: VTX may induce cardiotoxicity through inflammatory and apoptotic mechanism.

Aims:

I. To investigate the effect of VTX on the heart.

II. To understand the signaling and molecular mechanisms that account for the toxic effect of VTX on the heart.

METHODS

24 male albino rats were divided into 3 groups:

➢Control group (received i.p injection of normal saline)

➢Low dose of VTX group (received 50 mg/kg VTX by oral gavage)

➢High dose of VTX group (received orally 100 mg/kg VTX by oral gavage).

- **Histopathology studies (using H&E stain).**
- **Western blot analysis to measure protein expression.**
- **qPCR to measure gene expression.**
- **Biochemical assays.**

RESULTS

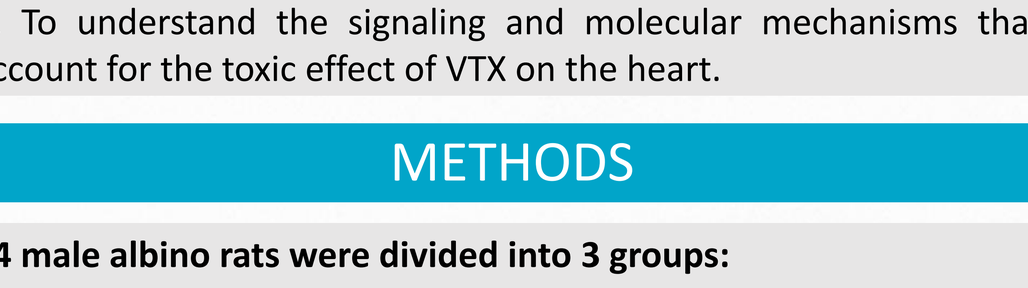

Figure 1: Light micrographs of the cardiac tissues (H&E stain; magnification 400×)
(A) Section of myocardium obtained from the control group. Note the normal and parallel myocardial fibers with cross-striation and regular nuclei. (B) Section of myocardium obtained from the group which received low dose VTX. Note the normal appearance of the myocardial fibers but with minimal nuclear enlargement. (C) Section of myocardium obtained from the group which received high dose VTX. Note the presence of a focus of myocardial damage associated with chronic inflammatory reaction (arrowhead).

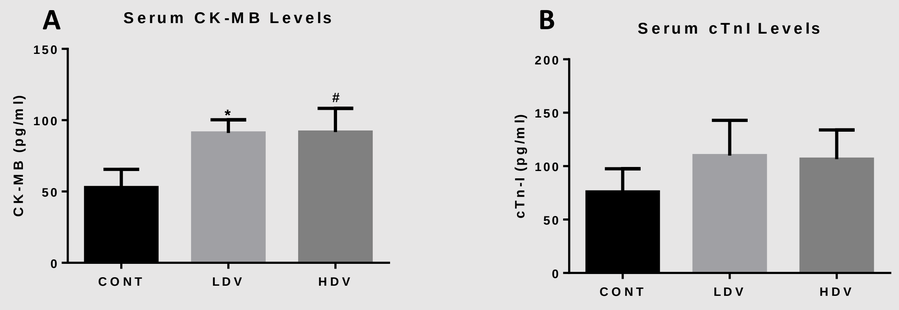

Figure 2: Plasma levels of cardiotoxicity markers
Plasma samples from different groups were analyzed for CK-MB & cTnI levels (A & B, respectively). Data are presented as mean ± SEM. Comparison between control group and LDV groups presented by *, while comparison between control HDV groups are presented by #; where # P< 0.05.

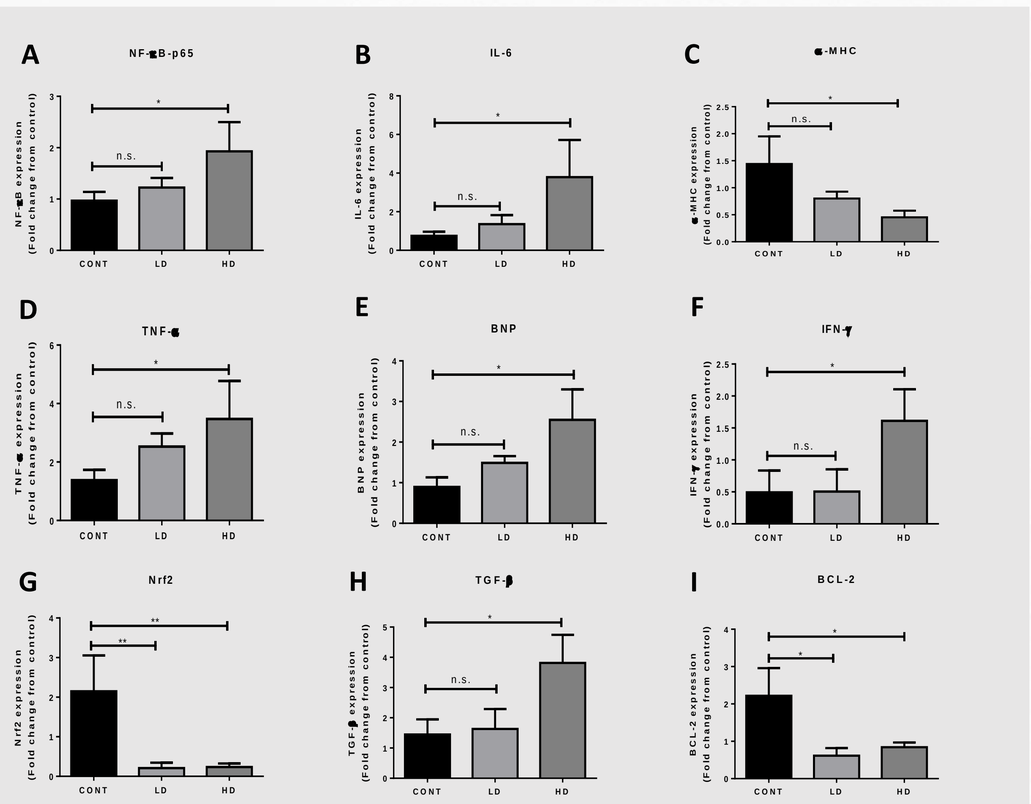

Figure 3: VTX induces the gene expression of inflammatory, oxidative stress, and apoptotic markers
Cardiac NF-kB-p65 (A), IL-6 (B), a-MHC (C), TNF-a (D) IFN-g (E) Nrf-2 (G) TGF-b (H) BCL-2 (I) mRNA levels were measured using quantitative RT-PCR method. Data are presented as mean ± SEM. *; where * P< 0.05 & ** P< 0.01, n.s. means no significant changes were observed.

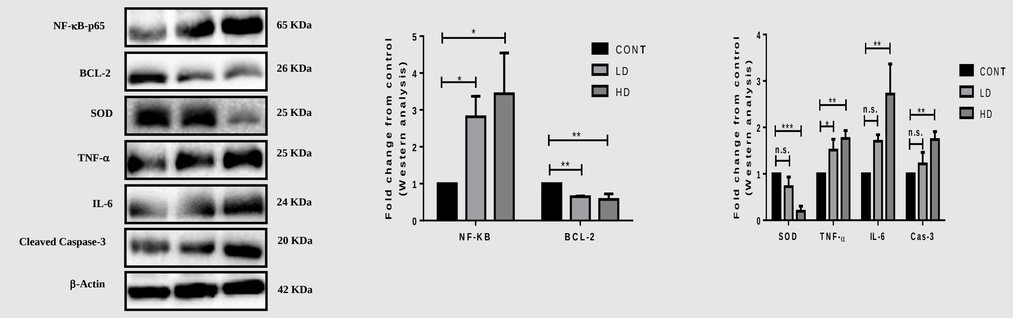

Figure 4: VTX activates apoptotic and inflammatory pathways
Western blot analysis of NF-kB-p65, BCL-2, SOD, TNF-a, & IL-6 in hearts from control, LD, & HD groups. Data are presented as mean ± SEM. where * P< 0.05, ** P<0.01 and *** P<0.001. n.s. means no significant changes were observed (P>0.05).

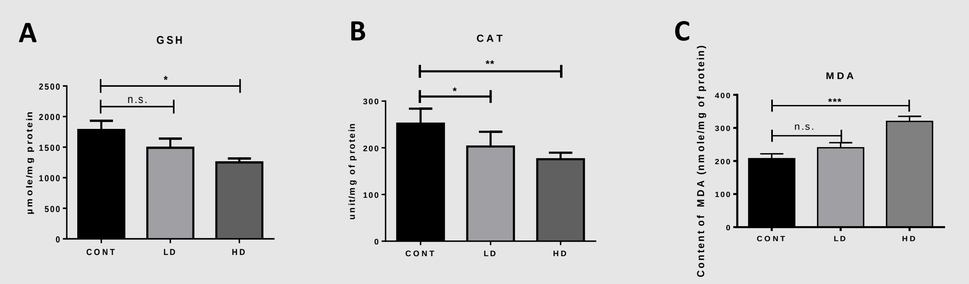

Figure 5: VTX reduces the anti-oxidants activity
Biochemical analysis to measure the activity of the antioxidants GSH (A), Catalase (B), and MDA (C). Data are presented as mean ± SEM. where * P< 0.05 ** P<0.01 and *** P<0.001. n.s. means no significant changes were observed (P>0.05).

DISCUSSION & CONCLOSIONS

To the best of our knowledge, this is the first study to report the cardiotoxic effect of VTX. Further studies are strongly needed to comprehensively understand the cardiotoxic effect of VTX.

REFERENCES

1. Davids MS, Hallek M, Wierda W, et al. Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia. *Clin Cancer Res*. 2018;24(18):4371-4379.
2. Wanchoo R, Bernabe Ramirez C, Barrientos J, Jhaveri KD. Renal involvement in chronic lymphocytic leukemia. *Clin Kidney J*. 2018;11(5):670-680.
3. Mahida, H., Gharia, B., Ugoeke, N., Maludum, O., Asif, A., & Calderon, D. (2018). Evaluation of cardiovascular adverse events associated with ibrutinib, venetoclax and idelalisib used in treatment of chronic lymphocytic leukemia.

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