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Sodium-glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin, does not ameliorate non-diabetic renal injury

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Introduction
The sodium-glucose cotransporter 2 (SGLT2) inhibitors were shown to have their protective effect on diabetic kidney disease and heart failure. It targets SGLT2 in renal proximal tubules and promotes glycosuria in type 2 diabetic mellitus, resulting in lowering blood glucose. However, its role remains uncertain in non-diabetic kidney disease. In this study, we investigated the effects of SGLT2 inhibitor, dapagliflozin (DAPA), on a mouse model of adriamycin (ADX)-induced nephropathy and adult zebrafish injury model.

Methods
ADX induced nephropathy model resulted in severe proteinuria and progressive glomerulosclerosis. Seven week old Balb/c mice were divided in five groups; 1) control with vehicle, 2) control with DAPA 3mg, 3) ADX (11.5mg/kg) control, 4) ADX (11.5mg/kg) +DAPA 1mg, 5) ADX (11.5mg/kg) + DAPA 3mg. With ADX injection, DAPA was administered via gavage for 2 weeks. Adult zebrafish were injected 40mg/kg of gentamicin (GM) or/and 3ug of DAPA via intraperitoneal injection. Dextran filtration assay was performed and by in situ hybridization, slc5a2, wt1b, pax2a, lhx1a, and fgf8a gene expressions were evaluated over kidney injury and regeneration.

Results
When compared to ADX control mice group, administration of DAPA did not alleviate proteinuria in ADX-induced nephropathy. In the kidney, ADX injection induced significant glomerular and interstitial injury, and SGLT2 inhibition did not attenuate the extent of renal injury. Gene and protein expressions of ED1, the macrophage marker in the kidney were significantly increased in the ADX control group. DAPA administration in ADX groups decreased macrophage infiltration in the renal medulla compared to ADX control group, whereas no significant difference was observed in the renal cortex. SGLT2 expressions were decreased in DAPA administration groups as expected. In adult zebrafish, GM-induced tubular injury was confirmed after 1 day and regeneration after 4 days by dextran filtration assay. Over this duration, slc5a2 gene expression was disappeared after 1 day and recovered after 5 days. wt1b and pax2a gene expressions were increased after 5 days of GM. wt1b and pax2a gene expressions were increased after 1 day of DAPA. DAPA did not recover slc5a2 gene expression after 5 days of GM injection and did not change wt1b and pax2a gene expressions during the regeneration.

Conclusion
From the results, dapagliflozin had no protective effect on ADX-induced kidney injury in mice model and GM-induced zebrafish injury model. However, interestingly DAPA improved renal medullary injury although it had no effect on renal cortex injury.