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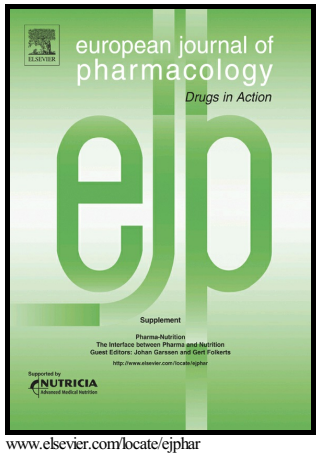

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ACCEPTED MANUSCRIPT

Precision medicine approach: Empagliflozin for diabetic cardiomyopathy in mice with aldehyde dehydrogenase (ALDH) 2*2 mutation, a specific genetic mutation in millions of East Asians

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Abstract

A vast majority of type-2 diabetic patients (~65%) die of cardiovascular complications including heart failure (HF). In diabetic hearts, levels of 4-hydroxy-2-nonenal (4HNE), a reactive aldehyde that is produced upon lipid peroxidation, were increased. We also demonstrated that in diabetic hearts, there is a decrease in the activity of aldehyde dehydrogenase (ALDH) 2, a primary detoxifying enzyme present in cardiac mitochondria. A single point mutation at E487K of ALDH2 in East Asians known as ALDH2*2 intrinsically lowers ALDH2 activity. We hypothesize that Empagliflozin (EMP), a sodium-glucose cotransporter (SGLT) 2 inhibitor, can ameliorate diabetic cardiomyopathy by decreasing hyperglycemia-mediated 4HNE protein adducts in ALDH2*2 mutant mice which serve as a precision medicine tool as they mimic ALDH2*2 carriers. We induced type-2 diabetes in 11-14 month-old male

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