Team systematically modifies glyceraldehyde derivative JX22 for improved anti-heart failure efficacy and safety

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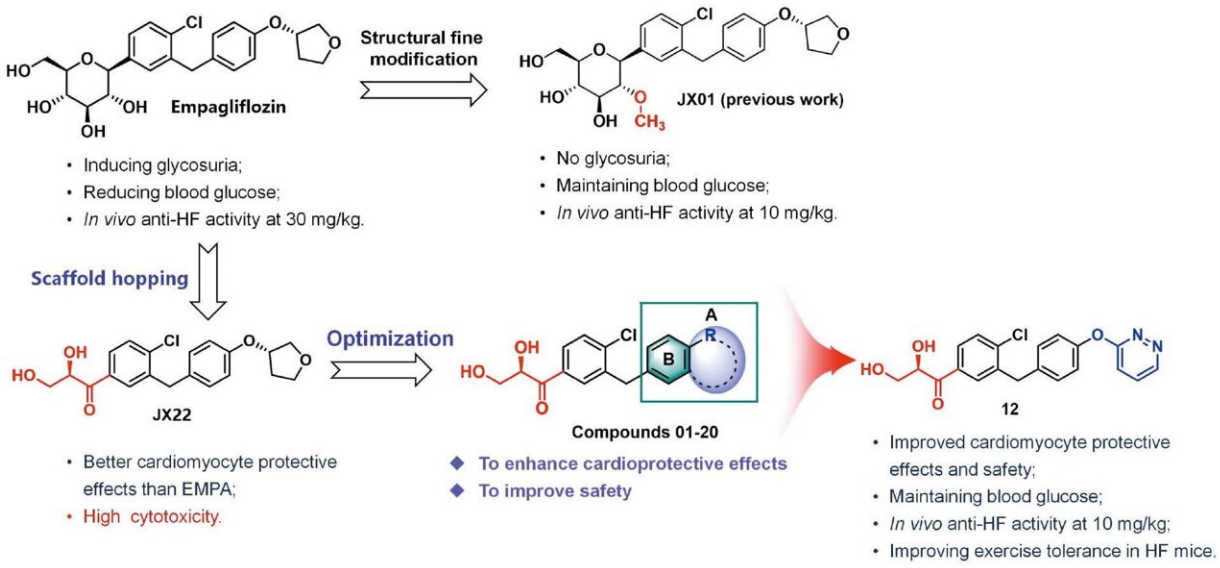

Structural repurposing of JX22 to develop new skeleton derivatives with anti-HF activity. Credit: *Acta Materia Medica* (2024). DOI: 10.15212/AMM-2024-0009

Sodium-glucose cotransporter 2 inhibitors are a class of glucose-lowering drugs known for robust cardiovascular protective properties. However, the side effects induced by sodium-glucose cotransporter 2 inhibition limit application in cardiovascular medicine.

Prior research showed that thoughtful structural modifications can

dissociate the anti-heart failure activity from glucose-lowering effects. Moreover, it was shown that the glyceraldehyde derivative JX22, developed by scaffold hopping from empagliflozin, exhibits a superior cardiomyocyte protective effect, albeit with increased cytotoxicity compared to empagliflozin.

In new research published in the journal *Acta Materia Medica*, researchers report that they have modified JX22 to enhance anti-heart failure efficacy and safety.

In this study, systematic structural modifications of JX22 were performed to enhance anti-heart failure efficacy and safety, while reducing glucose-lowering activity. Twenty glyceraldehyde-based derivatives were synthesized and compound 12 emerged as an optimal candidate by exhibiting an improved cytoprotective effect compared to JX22.

Compound 12 significantly inhibited the activity of NHE1 on the myocardial membrane, thereby maintaining intracellular ion homeostasis. In vivo efficacy results demonstrated that compound 12 at 10 mg/kg significantly ameliorated cardiac dysfunction, myocardial fibrosis, and exercise tolerance in isoproterenol-induced heart failure mice without a glucose-lowering effect.

Furthermore, compound 12 exhibited favorable safety profiles in single-dose toxicity and hERG inhibition tests, along with promising pharmacokinetic properties in mice.

This study not only underscores the potential of compound 12 for further investigation but also highlights the effectiveness of the scaffold hopping strategy.

More information: Xiao Li et al, Glyceraldehyde derivatives inspired

by empagliflozin as potential anti-heart failure agents independent of glucose-lowering effects, *Acta Materia Medica* (2024). DOI: 10.15212/AMM-2024-0009