

Title: Molecular Docking, Quantum Mechanics and Molecular Dynamics Simulation of Anti-CAD Drugs Against High-Risk Xanthine Dehydrogenase Variants Associated with Oxidative Stress Pathways

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Abstract: Xanthine dehydrogenase (XDH) contributes significantly to generating reactive oxygen species in coronary artery disease (CAD). XDH has been proposed as a therapeutic target, but its genetic variants could affect protein structure and drug response. We aimed to assess protein structure modification occur due to genetic variants and to screen 215 CAD drugs for their utility in personalized CAD treatment against the XDH variants. A series of computational methods were implemented to identify pathogenic variants that cause XDH structure instability localized at the con served regions contributing to functional significance. Then, the XDH structures with the pathogenic variants were modeled using two different approaches to select the best models for docking with the CAD drugs. Finally, the stability of the docked complexes and their ability to transfer electrons were evaluated using molecular dynamics (MD) simulations and quantum mechanics/molecular mechanics (QM/MM) calculation. Among 751 variants examined; R149C and Q919R showed high pathogenicity, localized in conserved regions could alter protein structure and function. Further, docking of CAD drugs against XDH (native, R149C and Q919R) showed vericiguat with higher affinity, ranging from -7.95 kcal/mol to -10.41 kcal/mol, than the well-known XDH inhibitor (febuxostat, -5.73 kcal/mol to -8.35 kcal/mol). This indicates that vericiguat will be effective in CAD treatment, regardless of the XDH variants. Additionally, MD simulation and QM/MM confirmed vericiguat stability and electron transfer ability to form hydrogen bonds with the XDH protein. In conclusion, vericiguat will be beneficial for the personalized treatment of CAD by inhibiting XDH variants. Additional clinical studies are necessary to confirm our findings.

Keywords: Coronary artery disease, Xanthine dehydrogenase, Genetic variants, Personalized treatment, Molecular modelling, Molecular dynamics simulation

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