Title: Hepatoprotective potential of *Nypa fruticans* leaves: Insights from integrated experimental and computational approaches

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Abstract: Ethnopharmacological relevance *Nypa fruticans* (NF) is traditionally used in Southeast Asia for the treatment of inflammatory and liver disorders. Its leaves contain phenolic and flavonoid compounds with antioxidant and anti-inflammatory properties; however, their hepatoprotective and antifibrotic potential remains insufficiently explored. Aim of the study This study assessed the hepatoprotective and antifibrotic effects of ethyl acetate and ethanol extracts of NF leaves in a CCl_4-induced liver fibrosis mouse model and examined their mechanisms through experimental and in silico analyses. Materials and methods Male mice with CCl_4-induced hepatic fibrosis were treated with graded doses of ethyl acetate and ethanol extracts of NF leaves. Biometric, biochemical, and histopathological parameters were assessed. Major metabolites were identified, and key phenolic and flavonoid compounds were evaluated via molecular docking (MD) with the TGF-β I receptor (PDB: 1VJY) and further validated via molecular dynamics simulation (MDS).Results NF leaf extracts significantly reduced serum liver enzyme levels (ALT, AST, and ALP) animproved liver histology, with the strongest effects observed at 400 mg/kg, confirming their hepatoprotective and antifibrotic activities. Molecular docking revealed CID 72276 as having the highest binding affinity (−12.354 kcal/mol) for the TGF-β I receptor, whereas molecular dynamics simulation revealed quercetin (CID: 5280343) as the most stable ligand, with the lowest RMSD (1.42 Å) and RMSF (0.766 Å).Conclusions *Nypa fruticans* leaf extracts demonstrated notable hepatoprotective and antifibrotic effects in a CCl_4-induced fibrosis model, likely via TGF-β/Smad pathway modulation. Computational analysis identified quercetin (CID 5280343) as the most promising lead, supporting its potential as a natural therapeutic for liver disease.

Key words: Liver fibrosis Nypa fruticans Hepatoprotective Histopathology Molecular dynamic simulation

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