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MITIGATION OF DRUG-INDUCED HEPATOTOXICITY BY NOVEL PHENOLIC ACID-ISONIAZID MUTUAL PRODRUGS: DESIGN, SYNTHESIS, KINETICS AND BIO EVALUATION

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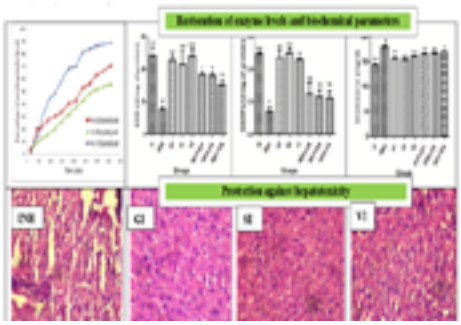
Aims & Objective: To overcome hepatotoxicity caused by long term use of anti-tubercular agent isoniazid (INH), a novel hepato-protective prodrug strategy was developed by combining INH with phenolic acids as antioxidant carriers for probable synergistic effect.

Methodology: INH was conjugated with antioxidant phenolic acids through a bioreversible amide linkage using Schotten Baumann technique. Synthesized prodrugs were characterized by spectral analysis and *in vitro* release kinetics was studied by HPLC. Hepatoprotective potential was evaluated in male Wistar rats by performing the liver function tests, oxidative stress markers and histopathology studies.

Results: Prodrugs resisted hydrolysis in acidic (pH 1.2), basic (pH 7.4) buffers and rat stomach homogenates whereas hydrolyzed significantly (56.03-88.62%) in intestinal homogenates over a period of 6h. All the prodrugs were effective in abating oxidative stress and re-establishing the normal hepatic physiology. Especially the effect of prodrugs of INH with gallic acid and syringic acid in restoring the levels of enzymes superoxide dismutase and glutathione peroxidase and abrogating liver damage was noteworthy.



Conclusion: The findings of this investigation demonstrated that the reported mutual prodrugs can add safety and efficacy to future clinical protocols of tuberculosis treatment.