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Synthesis And Pharmacological Screening Of Novel Piperine Analogs For Potential In Vitro Protection From Endoplasmic Reticulum Stress

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Abstract

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Background: The endoplasmic reticulum (ER) is the chief organelle involved in protein homeostasis. Perturbations to the ER protein folding machinery caused by hyperlipidemia, hyperglycemia or hypoglycemia has been shown to trigger ER stress and activate the unfolded protein response (UPR) as a defense mechanism. Accumulating evidences implicate the role of ER stress in the development of chronic kidney disease. Thus there is an urgent need for novel compounds, which have the ability to ameliorate ER stress to treat or prevent any organ damage. Among the natural compounds, piperine and its analogs have been reported to exhibit multiple pharmacological activities, however, the efficacy of piperine and its analogs against ER stress in kidney cells is still unknown. Thus, the goal of the current study is to synthesize a range of piperine analogs and screen them for pharmacological activity to relieve ER stress using an in vitro model of tunicamycin-induced ER stress in rat renal proximal tubular (NRK-52E) cells. Methods: To perform a structure-activity relationship study, several piperine analogs were prepared using piperic acid as a starting material. The structures of the obtained compounds were confirmed by liquid chromatography-mass spectrometry (LC/MS), differential scanning calorimetry (DSC), fourier transform infrared (FT-IR) and nuclear magnetic resonance (NMR). The in vitro ER stress model was developed using tunicamycin. Results: Several piperine analogs were synthesized and their structures were elucidated. The preliminary findings indicate that exposure to tunicamycin induces the expression of ER chaperone GRP 78 in NRK-52E cells. The MTT assay confirms the reduction in cell viability even with a low concentration of 1 ug/mL of tunicamycin for 15 minutes. The developed in vitro model will be used to evaluate the effect of piperine analogs on ER stress markers. Conclusion: The synthesis, structural elucidation and the results of the preliminary screening of selected piperine analogs will be presented.
Key Words: Piperine, Amide Piperine Analogs, ER stress, NRK-52E, Tunicamycin.