Template for Abstract

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Firstname Lastname[1,*], Firstname Lastname[2] and Firstname Lastname[1]
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[1]Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002,
[2]Departemnt of Biochemistry, Faculty of Sciences, Mahidol University, Bangkok 10330, Thailand
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ABSTRACT
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Objectives:.....
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Methods: .....
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Metformin Enhances Cisplatin-induced Cytotoxicity Through Oxidative Stress Mediated Mitochondrial Pathway in Cholangiocarcinoma Cells

Jaroon Wandee[1, 3*], Auemduan Prawan[1, 2], Laddawan Senggunprai[1, 2], Sarinya Kongpetch[1, 2] and Veerapol Kukongviriyapan[1, 2]

[1] *Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002,*

[2] *Cholangiocarcinoma Research Institute, Khon Kaen University, Khon Kaen 40002, Thailand.*

[3] *Current address: Faculty of Veterinary Science, Mahasarakham University, Mahasarakham 44000, Thailand.*

ABSTRACT

Introduction: Metformin (Met), a first-line drug for the treatment of diabetes, has antineoplastic activity in some cancers. Cholangiocarcinoma (CCA) is a biliary tract malignancy and has very poor prognosis. Chemotherapy plays an important role for the unresectable patients as a palliative treatment. It is, therefore, new drug or new strategy with more efficacy is required of the treatment of CCA.

Objectives: The present study investigated the chemosensitizing effect of Met on cytotoxicity in CCA cells, and examined underlying mechanism involved with the effect.

Methods: KKU-M156 and KKU-100 cells were used in the study. Cytotoxicity was assessed by acridine orange-ethidium bromide staining method. Reactive oxygen species (ROS) and mitochondrial transmembrane potential ($\Delta\psi m$) were analyzed by dihydroethidium and JC-1 fluorescent dyes. Cellular glutathione (GSH) and glutathione disulfide (GSSG) were measured by enzymatic assay. Protein expressions in association with cell death and antioxidant system were determined by western immunoblot.

Results: Met increased Cis-induced cytotoxicity in association with ROS generation, GSH redox stress and the loss of $\Delta\psi m$. Pretreatment with *N*-acetylcysteine and TEMPOL prevented Cis-induced cytotoxicity in association with suppression of ROS formation and prevention of the loss of $\Delta\psi m$. The combination of Met and Cis suppressed expression of Nrf2 and its downstream HO-1 proteins, and altered expression of Bcl2 family proteins and cytohrome c.

Conclusions: Met enhances the chemosensitivity of Cis in CCA cells is probably involved with increased oxidative stress mediated mitochondrial cell death pathway. Met may be a strategy to improve efficacy of the chemotherapeutic agents in the CCA treatment.

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Keywords: Chemosensitization, metformin, cisplatin, redox stress, cholangiocarcinoma