The iron-chelating drug M30 down-regulates carbon tetrachloride (CCl4)-induced hepatic oxidative stress, inflammation and apoptosis in vitro

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BACKGROUND/AIMS: The novel multifunctional brain permeable ironchelator M30 possesses neuroprotective activities against several insults applicable to various neurodegenerative diseases. However, the effect of M30 on CCl4 induced acute liver damage is still unknown. The aim of this study is to investigate whether the multifunctional drug M30 could ameliorate CCl4 induced hepatic injury in human HepG2 cell line. METHODS: HepG2 cells were grown in DMEM supplemented with 10 %fetal bovine serum and they were divided into control, CCl4, M30, and CCl4 + M30 co-treatment groups. M30 was pretreated for 2 h containing a final concentration at 5 lM. Then CCl4 was added with a final concentration at 2 ll/ml and incubated for 1 h. Finally, the cells were harvested and the cell viability was determined by colorimetric MTT assay based on conversion of MTT to blue formazan crystals by viable cells. In addition, the malondialdehyde levels were determined using a Bioxytech LPO-586TM kit, and real time PCR was also utilized to test the RNA expression levels of antioxidant enzymes, pro-inflammatory mediators and apoptotic markers. RESULTS: M30 significantly reduced CCl4 triggered cell death and MDA levels. Co-treatment of M30 and CCl4 up-regulated the expression levels of antioxidant enzymes catalase and glutathione peroxidase, which indicated that M30 reduced CCl4-induced oxidative stress and inhibited lipid peroxidation. In addition, administration of M30 attenuated hepatic inflammation triggered by CCl4 via inhibiting pro-inflammatory mediators, such as tumor necrosis factor alpha and interleukin-6. M30 also exhibited its anti-apoptotic activity by downregulating proapoptotic protein Bax, up-regulating anti-apoptotic protein Bcl-XL, as well as by recruiting Fas-associated death domain (FADD). CONCLUSION: M30 attenuates CCl4-induced HepG2 cellular damage through its antioxidant, anti-inflammatory and anti-apoptotic properties, which could serve as a potential functional drug to treat acute hepatotoxicity and chronic liver diseases such as non-alcoholic fatty liver disease and steatohepatitis.