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MIT-001 improves kidney tissue damage caused by fibrosis during renal ischemia-reperfusion.

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Objectives : Ischemia-reperfusion injury (IRI) is a well-known cause of progression to renal fibrosis, a major pathologic symptom of chronic kidney disease (CKD). Ischemia-reperfusion (IR) increases inflammatory stimuli as CKD progresses, leading to ferroptosis and fibrosis. MIT-001 was demonstrated to protect against necrosis and inflammation in virous organ injuries. In the present study, we evaluated whether MIT-001 improves CKD-induced renal fibrosis through an anti-inflammatory response and reduction of reactive oxygen species in an IRI mouse model, and we investigated the mechanisms involved.
Methods : C57BL/6 mice (eight weeks old, male) were divided into groups according to IR and MIT-001 administration. IR was induced via 24-h renal IRI. One (1d), three (3d), or seven days (7d) after MIT-001 treatment, kidney tissue and blood were collected. HK2 cell with TGF-β treatment are used for invitro studies.
Results : MIT-001 improved renal function and exhibited anti-inflammatory, anti-ferroptosis, and antifibrotic effects in the IRI model. In MIT-001-treated IRI 3d and 7d mice, blood urea nitrogen (BUN) and serum creatinine levels were reduced, while renal expression of F4/80, collagen IV, α-SMA, and TGF-β decreased, and E-cadherin expression increased. In TGF-β-exposed HK-2 cells, MIT-001 increased the mRNA expression of antioxidant and anti-ferroptosis-related genes (MnSOD, GPX4, and UCP1) in a dose-dependent manner. MIT-001 also suppressed TGF-β-induced ferroptosis and inflammation by increasing the expression of xCT, SLC7A11, and GPX4 proteins while reducing the expression of 4-HNE protein and mRNA. Furthermore, MIT-001 treatment decreased the expression of inflammation-related genes (OPN and MCP-1) and reversed the fibrosis-associated protein changes caused by TGF-β, increasing E-cadherin expression while reducing collagen IV, α-SMA, snail, and twist levels.
Conclusions : Our results confirmed that IR damages the kidneys and causes fibrosis. MIT-001 functions as a protector against IRI-induced renal fibrosis in IRI mice.

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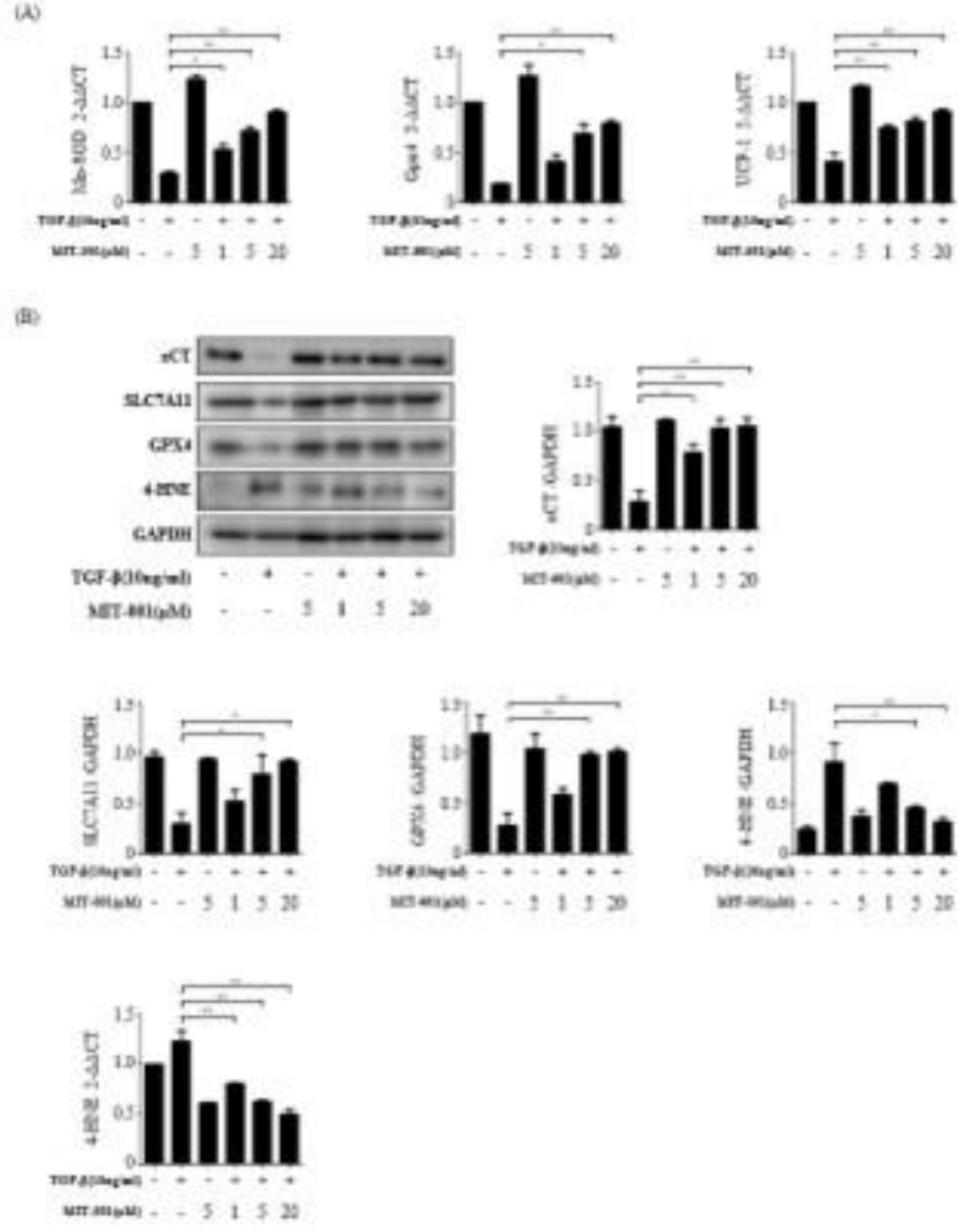

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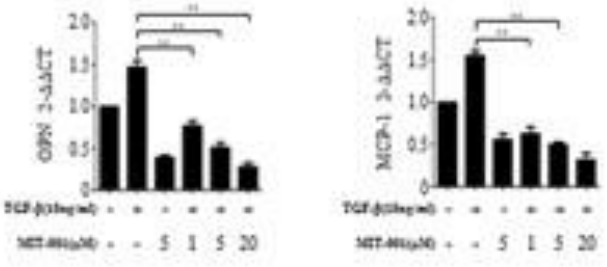

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