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Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

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Dicoumarol protects against kidney fibrosis by targeting caveolin-1 accelerated TGFRs degradation

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Objectives : Kidney fibrosis is characterized by disrupted cellular balance and excessive extracellular matrix (ECM) deposition, presenting the final expected outcome of chronic kidney diseases. Until now, few medications have been targeting kidney fibrosis. Emerging studies indicate caveolin-1, an essential membrane protein mediated by various member protein translocation, such as TGFβRs, has a promising antifibrotic effect linked with epithelial-mesenchymal transition (EMT). Our research aimed to explore dicoumarol's therapeutic effect and mechanism (DIC) against kidney fibrosis via suppressing EMT.
Methods : To establish the UUO model in vivo, the right ureter of rats was ligated with 4-0 silk, while the sham-operated group had no ligation. DIC was intragastric administration to rats at dosages of 2.5 and 5 mg/kg daily after operation. The sham and UUO groups received 0.5% CMC-Na. Rats were sacrificed, and tissues were collected on day 14 following western blotting and staining detection. In vitro, we chose the NRK52E cell line and stimulated it with TGFβ-1. Western blotting and qPCR detected the fibro-markers fibronectin, EMT relative markers a-SMA, vimentin, N-cadherin, and E-cadherin. The co-localization of TGFβRs and caveolin-1 was observed by immunofluorescence and co-IP.
Results : In the UUO experiment, administering DIC reverses fibrosis morphology change in the UUO model. The results of tissue section staining showed DIC could protect the kidney tissue lesions, mainly by decreasing the damage of kidney tubules and the production and accumulation of collagen, to achieve kidney protection. DIC effectively counteracted TGF-β1-induced morphological changes and reversed EMT-related protein expression, enhancing TGFβRs and caveolin-1 co-localization in vitro while not affecting kinase activities.
Conclusions : Our result offers a potential remedy by targeting caveolin-1 to constrain TGF-β signaling in the fight against fibrotic kidney diseases, implying that DIC may be the potential antifibrotic lead compound.

Fig1.jpg

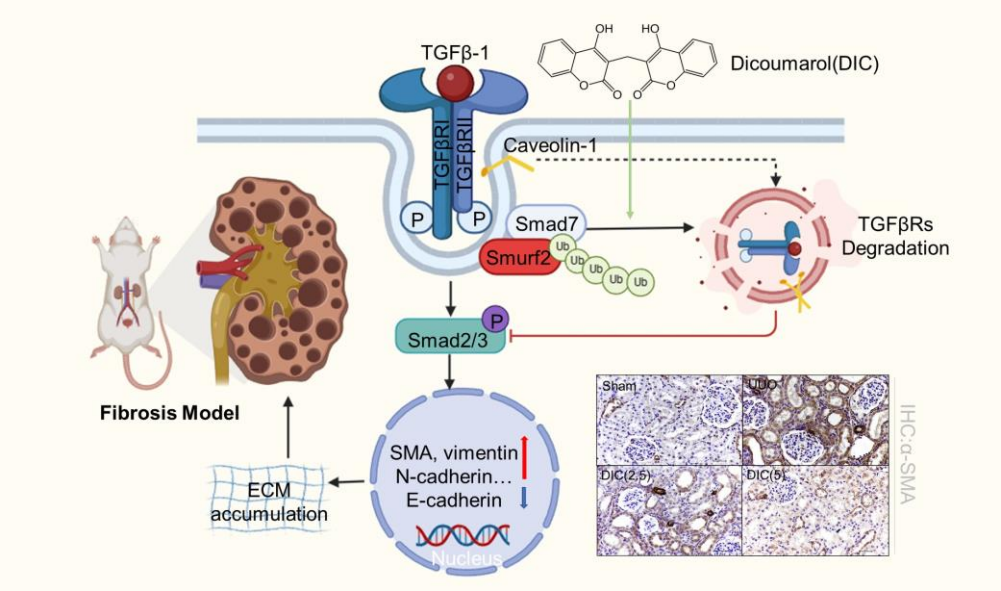
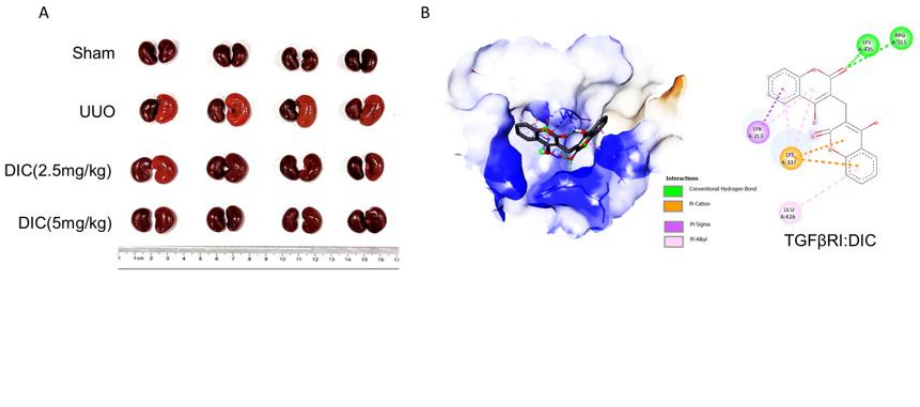

TGFβ-1
Dicoumarol(DIC)
OH
HO
TGFβRI
TGFβRII
Caveolin-1
P
P
Smad7
Smurf2
Ub
TGFβRs
Degradation
Smad2/3
P
Fibrosis Model
SMA, vimentin
N-cadherin…
E-cadherin
ECM
accumulation
Nucleus
Sham
UUO
DIC(2.5)
DIC(5)
IHC:α-SMA

Fig1.jpg


A
Sham
UUO
DIC(2.5mg/kg)
DIC(5mg/kg)
B
TGFβRI:DIC