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## **Protective effect against kidney fibrosis and tubule atrophy by Keap1 modulator**

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**Objectives :** Chronic kidney disease (CKD) is driven by metabolic disorders such as diabetes, obesity, and hypertension, with oxidative stress playing a key role in its progression. The Keap1-Nrf2 pathway regulates antioxidant defense, where Keap1 inhibits Nrf2 under normal conditions but releases it under oxidative stress, activating detoxifying genes. This study evaluates the effects of CV-01, a novel Keap1 modulator, in a CKD mouse model. By specifically targeting Keap1, CV-01 provides a distinct therapeutic approach compared to existing Nrf2 activators, potentially mitigating oxidative stress-induced kidney damage.

**Methods :** The kidney-protective effects of CV-01 were evaluated in a CKD mouse model. CKD was induced by feeding 0.2% adenine diet (AD) for 7 days. Mice were divided into five groups: Control, AD, AD+Vehicle, AD+CV-01 (50 mg/kg), and AD+CV-01 (100 mg/kg). CV-01 (Cureverse Inc.) was administered orally once daily, starting one day before disease induction. Kidney function was assessed by measuring blood urea nitrogen (BUN), cystatin C, and the urinary albumin-to-creatinine ratio (ACR). In vitro, HK-2 cells were treated with TGF- $\beta$  to mimic CKD, and reactive oxygen species (ROS) levels were measured using DCF-DA. Protein expression levels of Keap1, Nrf2,  $\alpha$ -SMA, and other key markers were analyzed via immunohistochemistry, immunofluorescence, and Western blotting.

**Results :** CV-01 significantly improved kidney function (BUN, cystatin C, ACR) and reduced tubular dilation and fibrosis in CKD mice. Keap1 expression was upregulated in the CKD model, correlating with tubular dilation and fibrosis. CV-01 treatment decreased Keap1 expression while upregulating Nrf2, HO-1, and NQO1, leading to reduced oxidative stress markers (8-OHdG, 4-HNE) and epithelial-mesenchymal transition markers ( $\alpha$ -SMA). In vitro, CV-01 attenuated TGF- $\beta$ -induced ROS production and enhanced Nrf2 nuclear translocation, further supporting its kidney-protective effects.

**Conclusions :** CV-01 protects against CKD by modulating the Keap1-Nrf2 pathway, reducing fibrosis, oxidative stress, and kidney dysfunction. These findings highlight CV-01's potential as a novel kidney-protective therapy.