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Renoprotective Effect of Celastrol in Diabetic Nephropathy in Rats: Implication of miRNA-192-5p, miRNA-21-5P, and Autophagy Activation

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Abstract

Background: Diabetic nephropathy (DN) is considered one of the significant complications of diabetes mellitus (DM), resulting in end-stage renal diseases. Current treatments carry a substantial residual risk of disease progression regardless of treatment. By modulating various molecular targets, pentacyclic triterpenoid celastrol demonstrated therapeutic characteristics for managing diabetes and other inflammatory diseases. Therefore, the current study aimed to examine whether celastrol has anti-inflammatory, antioxidant, and antifibrotic as natural compounds against experimental DN.

Method: Streptozotocin (55mg/kg) was utilized for inducing DN in a rat model. In kidney homogenate, relative miRNA-192-5p and miRNA-21-5p gene expressions were measured. In addition, real-time PCR was used to evaluate nuclear factor erythroid 2–related factor 2 (NRF-2), matrix metalloproteinase-2 (MMP-2), proapoptotic caspase-3, antiapoptotic Bcl-2, LC-3, and Beclin-1 relative gene expressions. Moreover, the transforming growth factor β1 (TGF- β1), LC-3, Bcl-2, and caspase-3 renal expressions were assessed using immunohistochemistry.

Key findings: Seven weeks of celastrol (1.5 mg/kg/day) treatment significantly ameliorated DN. Celastrol improves kidney functions. Moreover, celastrol treatment demonstrated a potent antioxidant effect. Celastrol treatment inhibited apoptosis by downregulating the renal expression of caspase-3, elevating the renal expression of Bcl-2, along with inducing autophagy by increasing LC-3 and Beclin-1 renal expression. Celastrol treatment improved renal fibrosis by decreasing TGF-ß1 and MMP-2 renal expression. These antifibrotic effects could be due to their ability to inhibit miRNA-192-5p as well as miRNA-21-5p expression in renal tissues.

Conclusion: Celastrol exerts a renoprotective effect by targeting miRNA-21 and miRNA-192, as well as their downstream pathways, such as autophagy, apoptosis, and fibrosis.

Keywords: Celastrol; diabetic nephropathy; miRNA-192-5p; miRNA-21-5p; TGF-β1; transforming growth factor β1.