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## Nimbolide abrogates cerulein-induced chronic pancreatitis by modulating Wnt/β-catenin/Smad in a Sirtuin 1-dependent way

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**Background and purpose:** Chronic pancreatitis (CP) is characterized by pancreatic inflammation and fibrosis, which leads to impairment of pancreas function. The present study was designed to investigate the possible mechanisms of chronic pancreatitis and the anti-inflammatory, antioxidant and anti-fibrotic effect of nimbolide (NB), active constituent of neem tree Azadirachta indica in cerulein-induced CP.

**Experimental approach and Key results:** Effect of nimbolide was investigated on cerulein 50 µg.kg-1.hr-1*6 exposures.-1day 3 days a week for 3 weeks induced CP model in Swiss albino mice. Nimbolide (0.3 and 1 mg/kg) and sirtuin 1 (Sirt1) inhibitor, nicotinamide (200 mg/kg), were given intraperitoneally daily for 21 days. Pancreatic function was assessed by biochemical evaluation including amylase and lipase levels. The deposition of collagen in pancreatic tissue was measured by using hydroxyproline assay, Picrosirius red and Masson's trichrome staining. The expression of collagen I, α-smooth muscle actin (SMA) and β-catenin in the pancreas tissue was evaluated using immunohistochemistry and immunofluroscence. NB treatment significantly reduced cerulein-induced CP by inhibiting Wnt/β-catenin signaling pathway including β-catenin, MMP7 and GSK3β. NB treatment remarkably decreased α-SMA, TGF-β1, MMP-2, fibronectin, p-smad-2/3 expression and collagen deposition in pancreatic tissue. However, the therapeutic effects of nimbolide against cerulein-induced CP were impaired by nicotinamide treatment. The levels of pro-inflammatory and pro-fibrotic cytokines such as TNF-α, IL-1β, IL-6 and TGF β1 were elevated by cerulein treatment; further, they were decreased by NB treatment. Additionally, NB was found to increase the expression of Sirt1 protein, which ultimately decreased the expressions of Smad2/3 and β-catenin signalling pathway proteins to attenuate cerulein-induced CP.

**Conclusion and implications:** Nimbolide attenuated cerulein-induced CP by activating Sirt1, which regulates Smad/β-catenin signaling pathways and it could be the novel therapeutic strategy for the treatment of CP associated fibrosis.

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