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Anti-viral mechanism of isosteviol derivative against hepatitis B virus

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An isosteviol derived compound, *ent*-16-oxobeyeran-19-*N*-methylureido (NC-8), was synthesized and its anti-hepatitis B virus (HBV) ability was investigated in human hepatoma cell lines. Treatment with NC-8 specifically inhibited viral gene expression and reduced the encapsidated viral DNA intermediates in Huh7 cells that express replicating HBV. To further assess the NC-8 inhibitory mode, four promoter regions of viral genes were isolated and the promoter-reporter assay was conducted. Results revealed that treatment with NC-8 potently attenuated all of the viral promoter activity in HBV-expressing Huh7 cells, but not in HBV non-expressing cells. Further examination of the roles of this anti-viral action in cellular signaling pathways showed that NC-8 inhibited the activity of NF-κB element containing promoter but enhanced the activities of AP-1 and ISRE containing promoters in HBV-expressing cells. Furthermore, treatment with NC-8 significantly eliminated NF-κB and TLR2 protein levels in a dose-dependent manner in HBV transfected Huh7 cells, but not in non-transfected cells. In electrophoretic mobility shift assay (EMSA), the binding activity of NF-κB to DNA element was enhanced in HBV transfected nuclear extracts of Huh7 cells, but treatment of NC-8 significantly reduced the DNA binding of NF-κB. Taken together, this study suggests that NC-8 mediates the antiviral effect by disturbing the replication and gene expression of HBV, as well as inhibiting the host TLR2/NF-κB signaling pathway.

Keywords: Isosteviol derivative; Hepatitis B virus; Human hepatoma cells; NF-κB; Toll-like receptor 2