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A novel cinnamyl sulfonamide hydroxamate derivative, NMJ-1 as a small molecule HDAC inhibitor with anti-cancer potential

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Cancer is caused by abnormal epigenetic modifications in addition to multiple genetic mutations. Histone deacetylase (HDAC) enzyme over expression has been found in many types of cancer, which is responsible for silencing of tumor suppressor genes and activation of proto oncogenes to oncogenes. Cinnamic acid derivatives were recently, found to have great anti-cancer potential through HDAC enzyme inhibition. Hence, the present study was based on modification of Cinnamic acid to cinnamyl sulfonamide hydroxamate derivative. The compound NMJ-1 was synthesized, purified and structurally confirmed by IR, GC-MS, and NMR and CHN-S elemental analysis. The HDAC enzyme inhibition activity for NMJ-1 was observed through whole cell HDAC assay and showed HDAC enzyme inhibition IC50 (3.89±0.17 μM). The cytotoxicity was studied by MTT assay using HCT-116 cancer cell-line in vitro and showed cell-growth inhibition IC50 (4.07±0.9 μM). The pro-apoptotic potential of NMJ-1 was observed throughG2/M arrest by cell-cycle analysis, increase in Annexing V binding and activation of cleaved caspase 3/7by flow cytometry. The acute oral toxicity study for NMJ-1 was performed according to OECD-425 guideline and was safe up to 2000 mg/kg dose in rats. DMH, a chemical carcinogen was administered weekly once i.p. at a dose of 20 mg/kg for 35 weeks to induce colon adenocarcinoma in rats. NMJ-1 and 5 FU were administered at dose of 50 mg/kg p.o. and 10 mg/kg i.p. respectively for 21 days in DMH induced colon cancer in rats. NMJ-1 and 5 FU administrations significantly reduced ACFs and tumor size. The histopathological study also showed reduction in number of tumors, tumor size and neutrophil infiltration with NMJ-1 and FU treatments. Our findings indicate that NMJ-1 has potential against colon cancer through HDAC enzyme inhibition and activation of intrinsic mitochondrial apoptotic pathway. Further detailed mechanistic studies are needed to confirm its anti-cancer efficacy.

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