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Antitumor Activity of Americanin A Isolated From the Seeds of *Phytolacca Americana* [POKE ROOT] by Regulating the ATM/ATR Signaling Pathway and the Skp2-p27 Axis in Human Colon Cancer Cells

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Abstract

The antiproliferative and antitumor activities of americanin A (1), a neolignan isolated from the seeds of *Phytolacca americana*, were investigated in human colon cancer cells. Compound 1 inhibited the proliferation of HCT116 human colon cancer cells both in vitro and in vivo. The induction of G2/M cell-cycle arrest by 1 was concomitant with regulation of the ataxia telangiectasia-mutated/ATM and Rad3-related (ATM/ATR) signaling pathway. Treatment with 1 activated ATM and ATR, initiating the subsequent signal transduction cascades that include checkpoint kinase 1 (Chk1), checkpoint kinase 2 (Chk2), and tumor suppressor p53. Another line of evidence underlined the significance of 1 in regulation of the S phase kinase-associated protein 2 (Skp2)-p27

axis. Compound 1 targeted selectively Skp2 for degradation and thereby stabilized p27. Therefore, compound 1 suppressed the activity of cyclin B1 and its partner cell division cycle 2 (cdc2) to prevent entry into mitosis. Furthermore, prolonged treatment with 1 induced apoptosis by producing excessive reactive oxygen species. The intraperitoneal administration of 1 inhibited the growth of HCT116 tumor xenografts in nude mice without any overt toxicity. Modulation of the ATM/ATR signaling pathway and the Skp2-p27 axis might be plausible mechanisms of action for the antiproliferative and antitumor activities of 1 in human colon cancer cells.