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The Novel Synthesized 2-(3-(Methylamino)phenyl)-6-(pyrrolidin-1-yl) quinolin-4-one (Smh-3) Induces G_2/M Phase Arrest and Mitochondria-dependent Apoptotic Cell Death Through Inhibition of CDK1 and AKT Activity in HL-60 Human Leukemia Cells

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2-Phenyl-4-quinolones series compounds have exhibited the influences of growth inhibitory on several human cancer cell lines. In this study, we investigated the effects of 2-(3-(methylamino)phenyl) -6-(pyrrolidin-1-yl)quinolin-4-one (Smh-3) on viability, cell cycle and apoptotic cell death occurred in different leukemia cell lines (HL-60, U937 and K562) in a dose- and time-dependent manner, but it did not obviously impair the viability of normal human umbilical vein endothelial cells (HUVEC) *in vitro*. The approximate IC_{50} was 103.26±4.59 nM for a 48-h treatment in HL-60 cells. Cell cycle analysis showed that 100 nM Smh-3 induced significant G2/M arrest in examined cells. Within 0, 12, 24 and 48 h treatment, Smh-3 inhibited the CDK1 activity and decreased protein levels of CDK1, cyclin A, cyclin B. Smh-3-induced chromatin condensation and DNA fragmentation were determined by DAPI and TUNEL staining. Cell apoptosis significantly reduced after pretreatment with a pan-caspase inhibitor (Z-VAD-fmk) and results indicated that Smh-3 induced apoptosis was mainly mediated by activation of caspase cascade in HL-60 cells. Results from colorimetric assays and Western blot analysis indicated that activities of caspase-9, caspase-7 and caspase-3 were promoted in Smh-3-treated HL-60 cells during cell apoptosis. Smh-3-induced apoptosis in HL-60 cells was accompanied by an apparent increase of ROS production, and protein levels of cytosolic cytochrome *c*, apoptotic protease activating factor-1 (Apaf-1) and apoptosis-inducing factor (AIF). Strikingly, Smh-3 induced apoptosis in HL-60 cells by simultaneously suppressing protein levels AKT activity, p-AKT, p-mTOR and p-BAD and inducing BAD protein levels. Taken together, we conclude that Smh-3 acted against leukemia cells *in vitro via* G2/M phase arrest, down-regulation of AKT activity and induction of mitochondria-dependent apoptotic pathways.