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Induction of Apoptosis by Withaferin A in Human Leukemia U937 Cells through Down-Regulation of Akt Phosphorylation

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Withaferin A, a major chemical constituent of *Withania somnifera*, has been reported for its tumor cell growth inhibitory activity, antitumor effects, and impairing metastasis and angiogenesis. The mechanism by which withaferin Ainitiates apoptosis remains poorly understood. In the present report, we investigated the effect of withaferin A on the apoptotic pathway in U937 human promonocytic cells. We show that withaferin A induces apoptosis in association with the activation of caspase 3. JNK and Akt signal pathways play crucial roles in withaferin A-induced apoptosis in U937 cells. Furthermore, we have shown that overexpression of Bcl-2 and active Akt (myr-Akt) in U937 cells inhibited the induction of apoptosis, activation of caspase 3, and PLC-g1 cleavage by withaferin A. Taken together, our results show that the activity of withaferin A to modulate multiple components in apoptotic response of human leukemia cells and raise the possibility that combined interruption of withaferin A and JNK and/or Akt-related pathways may represent a novel therapeutic strategy in hematological malignancies.

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Rottlerin Induces Heme Oxygenase-1 through ROS generation, p38 and Akt Phosphorylation and Nrf2/ARE Activation in Human Colon Cancer HT29 Cells

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Heme oxygenase-1(HO-1) is a cytoprotective enzyme activated by various reagents and we examined the ability of rottlerin, the major constituent of *Mallotus phillippinensis*, to upregulate HO-1 expression in human colon cancer HT29 cells. We demonstrate that rottlerin induces HO-1 expression in a concentration- and time-dependent manner. The inhibition of intracellular ROS production by N-acetylcysteine (NAC) and glutathione (GSH), results in a decrease in rottlerin-dependent HO-1 expression. Pharmacological inhibitors of phosphatidylinositol 3-kinase and p38 attenuate rottlerin-induced HO-1 expression. In addition, HT29 cells treated with rottlerin exhibit activation of p38 and Akt. Rottlerin also upregulates Nrf2 levels in nuclear extracts and increases ARE-luciferase activity.However, rottlerin-induced HO-1 expression is PKCδ independent. The present study strongly suggest that up-regulation of HO-1 by rottlerin through the ROS-p38, Akt-Nrf2-ARE signaling