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Analysis of apoptosis signaling pathway in human cancer cells by codeinone, a synthetic derivative of codeine.

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We have recently found that codeinone, an oxidation metabolite of codeine, induced apoptosis, characterized by internucleosomal DNA fragmentation and mitochondrial cytochrome c release in HL-60 human promyelocytic leukemic cell lines, most effectively among 10 opioids. These findings prompted us to investigate whether codeinone induces apoptosis in other human cancer cells and possible changes in mitochondrial enzyme. FACS analysis demonstrated that codeinone induced the production of ANNEXIN-positive apoptotic cells in three different human cancer cells (HL-60, MCF7, A549). The apoptotic cells were visualized by microscopical observation after staining with Hoechst (H)-33342. Fluorometric assay showed that codeinone time-dependently activated caspase 3 and caspase 9, but not caspase 8, suggesting the activation of intrinsic apoptotic signaling pathway via mitochondria. Western blot analysis demonstrated that codeinone enhanced the Pro-apoptotic Bax protein expression, but reduced the anti-apoptotic Bcl-2 protein expression. Codeinone did not significantly change the manganese superoxide dismutase (MnSOD) activity nor its mRNA expression. This apoptosis-inducing activity, in conjunction with antinociceptive activity, further substantiated the antitumor potential of codeinone.