

**Abstract:**

Khat is the *Celastraceus edulis* plant, a flowering evergreen tree or large shrub, which grows in the Horn of Africa and southwestern Arabia. Khat use has been associated with development of oral cancer, but its molecular effects remain controversial. This study describes a novel cytotoxic effect of whole khat extract on three leukemia cell lines. Cells were exposed to khat extract and harvested for analysis by fluorescent and electron microscopy, trypan blue exclusion, as well as immunoblotting to characterize the mode of cell death. In a separate series, cells were pretreated with a panel of caspase inhibitors for possible inhibitory effects. Khat induced a rapid cell death effect in HL-60, Jurkat, and NB4 cells that occurred within 2 h of exposure. The treated cells retained their ability to exclude trypan blue dye, a key feature in the apoptotic process. Exposed cells consistently developed morphological features of manifest apoptosis. Z-VAD, a pan-caspase inhibitor, completely inhibited toxic activity for up to 8 h, with partial inhibition by other caspase-specific agents. Western blot analysis showed specific cleavage of caspase-3 in khat-exposed cells. This study shows that khat induces cell death by apoptosis in a process sensitive to inhibition by caspase inhibitors, suggesting that subcellular interactions could be of particular relevance for the biological effects of khat in the cell death process and possibly carcinogenesis.