The aim of the study was to investigate the molecular mechanisms by which pipoxolan exerts apoptotic activity in human oral cancer cells. Pipoxolan reduced the cell viability and induced apoptosis in oral squamous cell carcinoma (OSCC) cell lines, TW206 and HSC-3. The effects of pipoxolan on the proliferation of cancer cells and on the distribution of cells within different phases of the cell cycle were investigated using a MTT assay and a flow cytometer, respectively. The effect of pipoxolan on the apoptosis of cancer cells was investigated using flow cytometer. Following exposure of TW206 cells to pipoxolan, there is a time-dependent decrease in the mitochondrial membrane potential and an increase in the reactive oxygen species (ROS). Pipoxolan treatment caused a time-dependent increase Fas/CD95, cytosolic cytochrome *c*, active form of caspase-8, -9 and -3, hydrolysis of PARP, Bax, and decrease of Bcl-2. Apoptosis was associated with an increased Bax/Bcl-2 ratio. Pipoxolan also suppressed the expressions of PI3K and phosphorylation of Akt. This is the first report confirming the anti-cancer activity of pipoxolan against human OSCC TW2-6 and HSC-3. Intracellular ROS seem to play a key role in the pipoxolan-induced apoptosis, since high levels of ROS were produced early in the drug treatment. Apoptosis was significantly abrogated by the free radical scavenger N-acetyl-L-cysteine (NAC). Also, pipoxolan-induced caspase-8, -9 an -3 activities can be blocked by pan-caspase inhibitor (Z-VAD-FMK). The abovementioned data suggest that pipoxolan acted against TW206 and HSC-3 in vitro via both intrinsic, extrinsic apoptotic signaling pathways, and exhibited in PI3K/Akt signaling pathway.