Inhibition of Wnt/β-catenin signaling mediates ursolic acid-induced apoptosis in PC-3 prostate cancer cells

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Abstract:
Background: Ursolic acid, a pentacyclic triterpenoid, is known to exert antitumor activity in breast, lung, liver and colon cancers. Nonetheless, the underlying mechanism of ursolic acid in prostate cancer cells still remains unclear. To investigate the antitumor mechanism, the apoptotic mechanism of ursolic acid via Wnt/β-catenin signaling was examined in PC-3 prostate cancer cells.

Methods: Cytotoxicity assay, flow cytometry, immunofluorescence assay and western blotting were performed.

Results: Ursolic acid showed cytotoxicity against PC-3, LNCaP and DU145 prostate cancer cells with IC₅₀ of 35 µM, 47 µM and 80 µM, respectively. Also, ursolic acid significantly increased the number of ethidium homodimer stained cells and apoptotic bodies, and dose-dependently enhanced the sub-G1 apoptotic accumulation in PC-3 cells. Consistently, western blotting revealed that ursolic acid effectively cleaved poly (ADP-ribose) polymerase (PARP), activated caspase-9 and -3, suppressed the expression of survival proteins such as Bcl-XL, Bcl-2 and Mcl-1, and upregulated the expression of Bax in PC-3 cells. Interestingly, ursolic acid suppressed the expression of Wnt5α/β and β-catenin, and enhanced the phosphorylation of glycogen synthase kinase 3 β (GSK3β). Furthermore, the GSK3β inhibitor SB216763 or Wnt3a-conditioned medium (Wnt3a-CM) reversed the cleavages of caspase-3 and PARP induced by ursolic acid in PC-3 cells.

Conclusions: Our findings suggest that ursolic acid induces apoptosis via inhibition of the Wnt5/β-catenin pathway and activation of caspase in PC-3 prostate cancer cells. These results support scientific evidence that medicinal plants containing ursolic acid can be applied to cancer prevention and treatment as a complement and alternative medicine (CAM) agent.

Key words:
ursolic acid, apoptosis, caspase, Wnt/GSK3β/β-catenin signaling

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