Letter to the Editor

Compound MMH02 Possesses Toxicity Against Human Cancer Cells With Sparing of Normal Monocytes

For cancer treatment with cytotoxic agents, the major dose-limiting factor is their toxicity to normal cells and tissues. This safety consideration is particularly critical in the elderly cancer patients, as they are known as a less-tolerant population. Leukemia is the most common hematological malignancy with high risk of relapse after treatment. Pancreatic cancer remains a disease with unfavorable clinical features, including difficulty in early diagnosis, rapid progression, and resistance to chemotherapy and radiotherapy. Similar poor clinical outcome is noted in esophageal cancer, hepatoma, and locally advanced cervical cancer. Clearly, development of novel agents against these devastating malignancies with less toxicity is urgently needed in clinical practice.

In this study, we isolated a novel compound from fruiting body of Antrodia cinnamomea, namely, Lanosta-8,24-dien-3β,15α,21-triol (chemical formula: C_{30}H_{50}O_{3}; molecular weight, 458) (Fig. 1). We thereby designated this novel compound as MMH02 and reported that MMH02 could inhibit the viability of selective types of cancer cells but not normal monocytes.

As for results, MMH02 markedly inhibited the growth of human leukemia U937, pancreatic BxPc-3, esophageal HA22T/VGH, and cervical HeLa cancer cells, but not ovarian adenocarcinoma SKOV-3 cells, by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. The growth inhibitory rates for these cancer cells ranged from 48.5% to 99.8%. In leukemic U937 cells, it resulted in a unique pattern of cell cycle distribution, including hypoploidy, G2/M arrest, and polyploidy (Fig. 2). The modes of cell death in U937 cells include apoptosis and mitotic catastrophe. For apoptosis, MMH02 induced oligonucleosomal fragmentation of genomic DNA, a hallmark of apoptosis, noted by DNA electrophoresis (Fig. 3). Estimation of apoptotic amount by the hypoploid population demonstrated in DNA histogram shows an apoptotic percentage up to 51.3%. MMH02 did not reduce the mitochondrial transmembrane potential, indicating a mitochondria-independent pathway. Caspase 3 and pan-caspase inhibitors could block the camptothecin-induced growth inhibition but not that induced by MMH02. Moreover, the expression of caspase 3 and 8 was not altered by MMH02. Taken together, MMH02 may induce apoptosis in a caspase-independent pathway. MMH02 might also induce mitotic catastrophe, another mode of cell death, according to the development of both distinct morphological feature and polyploidy cells. Cell proliferation assessed by clonogenicity was also inhibited in U937 cells. In pancreatic...
cancer BxPc-3 cells, MMH02 induced extensive apoptosis with up to 57.1% ± 3.5% hypoploid population noted. Intriguingly, only slight viability inhibition by MMH02 (less than 10%) was noted in human normal monocytes isolated from peripheral blood mononuclear cells, the normal counterpart of myeloid leukemic cells.

In conclusion, MMH02 possesses preferential cytotoxicity against human leukemia, pancreatic cancer, esophageal cancer, hepatoma, and cervical cancer cells without toxicity to normal monocytes. The in vivo experiment for validation of in vitro results and examination of normal organ toxicity is underway.

References


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