Enhanced inhibition of lung adenocarcinoma by combinatorial treatment with indole-3-carbinol and silibinin in A/J mice.

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Source

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Abstract

In earlier studies, we demonstrated the efficacy of indole-3-carbinol (I3C) against lung adenocarcinoma in A/J mice. However, these effects were accompanied by reductions in body weight gain. We therefore assessed if combinations of low doses of I3C with silibinin could inhibit lung tumorigenesis without causing undesirable side effects. In in vitro assays with A549 and H460 lung cancer cells, exposure of the cells to a mixture of low concentrations of I3C (50 μM) plus silibinin (50 μM) for 72 h caused inhibition of cell growth and extracellular signal-regulated kinase (ERK) and Akt activation and induction of apoptosis, whereas the individual agents did not have any effect. In mice pretreated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and given I3C (10 μmol/g diet) plus silibinin (7 μmol/g diet), multiplicities of tumors on the surface of the lung and adenocarcinoma were reduced by 60 and 95%, respectively. The individual effects of I3C and silibinin were relatively weaker: 43 and 36% reductions, respectively, in the multiplicity of tumors on the surface of the lung and 83 and 50% reductions, respectively, in the number of adenocarcinoma. Also, the expression of phospho-Akt, phospho-ERK and cyclin D1 and poly (ADP-ribose) polymerase cleavage were strongly modulated by I3C plus silibinin than by I3C or silibinin alone, suggesting that the chemopreventive activities of the mixture could be mediated, at least partly, via modulation of the level of these proteins. Taken together, our findings showed that mixtures of I3C and silibinin are more potent than the individual compounds for the chemoprevention of lung cancer in A/J mice.