



Pulmonary delivery of curcumin and quercetin nanoparticles for lung cancer – Part 2: Toxicity and endocytosis

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Highlights

- Nebulized combination NPs are more effective to kill A549 compared to single NPs.
- Combination with lower Cur-NPs fraction was more cytotoxic towards A549.
- Direct nebulization of NPs did not induce appreciable inflammatory marker expressions.
- Clathrin-mediated endocytosis is responsible for trafficking both NPs into A549 cells.

Abstract

The delivery of polyphenol compounds via inhalation to treat lung cancer is attractive to enable high drug concentration in the tumor cells. Although polyphenols such as curcumin (Cur) and quercetin (Que) have shown promising abilities to kill cancer cells, their applications were hampered due to poor aqueous solubility and limited physicochemical stability. Therefore, the aim of the present study is to investigate the effect of inhaled curcumin nanoparticles (Cur-NPs) and quercetin nanoparticles (Que-NPs) on the anti-cancer activity using air-liquid interface (ALI) culture of A549 alveolar epithelial cells. Nebulization of both Cur-NPs and Que-NPs in a combination of various ratios was more effective in killing A549 cells as compared to Cur-NPs alone and Que-NPs alone formulations. Among different combination ratios, it is found that formulations with higher Que ratio were more effective to induce apoptosis, ATP reduction, ROS generation and MMP loss in A549 cells. This is also followed by high expression of cytochrome C release and caspases (3 and 9). Nebulized Cur-NPs and Que-NPs in combination also led to an increase in the expression Bax (pro-apoptotic protein), as confirmed with Western blot. In general, the toxicity follows a decreasing trend: Cur-NPs: Que-NPs (1:4) > Cur-NPs: Que-NPs (2:3) > Cur-NPs: Que-NPs (3:2) > Cur-NPs: Que-NPs (4:1) > Cur-NPs only > Que-NPs only. In addition, all NPs were internalized via predominantly clathrin-mediated endocytosis, indicating that both Cur-NPs and Que-NPs were up-taken by cells in a similar endocytic pathway. In conclusion, the combination formulations of Cur-NPs and Que-NPs could be considered an alternative treatment for lung cancer through nebulization.

Graphical abstract