

Title : Membrane Permeabilization and Cytotoxicity of Natural and Synthetic Compounds as Potential Therapeutic Drugs.

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ABSTRACT

Membrane disruption is a key mechanism used by several natural and synthetic compounds to exert biological effects or induce cytotoxicity. This mechanism is often explored to identify potential drug candidates by focusing on analyzing the interaction between compounds and the cell membrane, as well as their ability to alter membrane structures, leading to cell death. This study investigates the membrane permeabilization properties of selected natural and synthetic compounds, including curcumin, extracts from *Curcuma longa*, and the synthetic 78-molecule (benzo[a]phenazine), which were previously reported to exhibit some biological activities. The study employed a fluorescence leakage assay using liposomes as a model for cell membranes. The liposomes were composed of POPE:POPC (1:1), which are common phospholipids found in cell membranes, and encapsulated with 5,6-carboxyfluorescein (CF) fluorescent dye at 80 mM. The results indicated that CF leakage from liposomes increased significantly upon the addition of curcumin, while no substantial leakage was observed with the 78molecule. Furthermore, the cytotoxicity of the compounds was tested on A549 lung cancer cells using the MTT assay, with gefitinib as a drug reference. Additionally, the cytotoxicity of the new strain of curcuma has been tested. The IC50 values of *Curcuma globulifera* extracted with various solvents, including Hexane, MeOH, and EtOAc, were found to be $79.25 \pm 35.0 \mu\text{g/mL}$, $75.98 \pm 19.9 \mu\text{g/mL}$, and $85.18 \pm 20.5 \mu\text{g/mL}$, respectively. The IC50 values for gefitinib, 78-molecule and curcumin were determined to be $5.48 \pm 0.7 \mu\text{M}$, $9.54 \pm 0.5 \mu\text{M}$ and $20.89 \pm 1.4 \mu\text{M}$, respectively, suggesting that gefitinib and 78-molecule was more effective in inhibiting A549 cell growth than curcumin and *C. globulifera* extracts. However, the membrane permeabilization did not correlate with cytotoxicity, possibly due to other complex mechanisms in cells. Overall, *Curcuma* plants, curcumin and 78molecule could still be beneficial for pharmaceutical research, offering potential for drug development.

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