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A hydroalcoholic extract from the leaves of *Nerium oleander* inhibits glycolysis and induce selective killing of lung cancer cells

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Background: *Nerium oleander* is an ornamental shrub used in traditional medicine for treating tumors and skin diseases. Several extracts from *Nerium oleander* containing cardiac glycosides have exhibited anticancer effects and one of them has entered Phase I Clinical trials for the treatment of cancer. In this communication, we have assessed the selective anticancer activity of a hydroalcoholic extract from the leaves of *Nerium oleander* and have evaluated possible mechanisms involved in this activity.

Methods: Fresh leaves of *Nerium oleander* were extracted with ethanol:water (1:1) at 60°C for 1 hour by using an ultrasound water bath apparatus. Ethanol was eliminated in a rotary vacuum evaporator and the remaining water solution was lyophilized with an extraction yield of 2.3%. The cell viability MTT assay was performed in the A549 human lung cancer cell line and the MRC5 human non-cancer cell line to assess the selective anticancer activity of the *Nerium oleander* extract. The pro-oxidant activity of the extract was evaluated in A549 cancer cells in the presence and absence of the antioxidants *N*-acetylcysteine (NAC) and Mn(III)tetrakis (1-methyl-4-pyridyl)porphyrin (MnTMPyP) by using the MTT assay. Glycolysis inhibition was assessed by measuring glucose and lactate concentrations in A549 cells exposed to the *Nerium oleander* extract.

Results and Discussion: After treatment with the *Nerium oleander* extract, cell viability in cancer cells was lower than that in non-malignant cells, with an IC₅₀ value of 0.26 ± 0.04 µg/ml in A549 cells and 1.65 ± 0.02 µg/ml in MRC5 cells. Pretreatment of A549 cells with NAC prevented the cytotoxic activity of the extract, but only to some extent, therefore suggesting that reactive oxygen species do not play a major role in the anticancer activity of the extract. The levels of glucose consumed by A549 cancer cells decreased markedly in the presence of the *Nerium oleander* extract. Likewise, lactate production was drastically reduced in A549 cells exposed to the extract. These results indicate that this extract inhibits glycolysis and suggest that glycolysis inhibition may play an important role in its selective anticancer activity.

Conclusion: A hydroalcoholic extract from the leaves of *Nerium oleander* induces selective killing of lung cancer cells. Because the activation of glycolysis plays an important role for the survival of cancer cells, the inhibition of glycolysis may explain why cancer cells are more vulnerable than non-malignant cells to the cytotoxic activity of this extract.