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Sclareol, a natural compound, inhibits P-glycoprotein activity in cancer cells

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P-glycoprotein (P-gp) is often expressed at the cellular membrane of cancer cells where it plays a significant role in protecting cancer cells from extracellular assault. It works as an export transporter for many substrates - xenobiotics including chemotherapeutics. Several generations of P-gp inhibitors have been developed and studied but they have not yet been introduced into clinics. The most promising fourth-generation comprises natural compounds. In this study, we evaluated the potential of sclareol, a naturally occurring labdane diterpene, to inhibit P-gp activity in human glioblastoma (U87, and its resistant variant U87-TxR with P-gp overexpression) and non-small cell lung carcinoma (NCI-H460, and its resistant variant NCI-H460/R with P-gp overexpression) cell lines. To that end, we used the accumulation assays of fluorescent P-gp substrates (rhodamine 123 and doxorubicin) that were analyzed by flow cytometry. An increase in the accumulation of the P-gp substrate corresponds to the level of P-gp activity suppression. Our results showed that simultaneous application of sclareol (20 μM and 50 μM) with either rhodamine 123 (5 μM) or doxorubicin (20 μM) significantly increased their accumulation in resistant cells (U87-TxR and NCI-H460/R) than in their corresponding sensitive cells (U87 and NCI-H460). The doxorubicin accumulation was also considerably increased in sensitive U87 cells implying that sclareol may interact with doxorubicin through other mechanisms in glioblastoma cells (not only by P-gp inhibition). Further investigations are envisioned to reveal the mechanisms behind sclareol and doxorubicin interaction in glioblastoma cells.

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