# INTERACTION OF (+)-STREBLOSIDE AND ITS DERIVATIVES WITH $NA^+/K^+$-ATPASE AND OTHER TARGETS

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(+)-Strebloside, a cardiac glycoside derived from *Streblus asper* Lour. (Moraceae), showed potential antitumor activity through inhibiting $Na^+/K^+$-ATPase, NF-κB activation, and mutant p53 expression. It displayed in vivo activity when immunodeficient NCr *nu*/*nu* mice implanted with hollow fibers containing MDA-MB-231 or OVCAR3 cells were treated (i.p.) daily with this compound at doses of 5.0 mg/kg for four days, but no obvious side effects were observed, even at the high dose of 30 mg/kg used. The hydroxy and formyl groups and the lactone unit substituted, respectively, at the C-14, C-10, and C-17 positions, were found to be important in the mediation of its cytotoxicity and in interacting with $Na^+/K^+$-ATPase, for which detailed information has not been reported. Also, the potential binding of this cardiac glycoside to other molecular targets has not been investigated thus far. Hence, docking profiles for (+)-strebloside and some of its derivatives and $Na^+/K^+$-ATPase and several other molecular targets, including FIH-1, HDAC, KEAP1 and MDM2 (negative regulators of Nrf2 and p53, respectively), NF-κB, and PI3K, have been investigated and compared with those for digoxin. The docking results showed that, similar to digoxin, (+)-strebloside and several of its derivatives bind to $Na^+/K^+$-ATPase, and the docking scores were found to correlate well to their cancer cell cytotoxicity. While (+)-strebloside and digoxin interact with FIH-1, these two compounds and their aglycones, strophanthidin and digoxigenin, bind to KEAP1 and MDM2, and (+)-strebloside and the aglycones also dock to the active pocket of PI3K. Thus, (+)-strebloside may target directly HIF-1, Nrf2 and p53 protein-protein interaction, $Na^+/K^+$-ATPase, and PI3K to mediate its antitumor activity. Nrf2 is a promising target for infection, and HIF-1α and PI3K have been defined as the key proteins of the tumor microenvironment, targeting cancer immunotherapy and relapse problems. Thus, (+)-strebloside could be investigated further as p53/MDM2 interactive- and tumor microenvironment-targeted cancer chemotherapeutic agents. This cardiac glycoside seems to be more promising for potential anticancer drug development than digoxin, as evidenced by its more potent cancer cell cytotoxicity, lower toxicity, and potential binding to PI3K when compared with the latter compound.

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