Med Aromat Plants 2018, Volume 7
DOI: 10.4172/2167-0412-C4-027

The potential deoxycytidine kinase inhibitory activity of amaryllidaceae alkaloids: an in silico approach

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Plants of the Amaryllidaceae family have been under intense scrutiny for the presence of a couple of alkaloidal secondary metabolites with endued cytotoxic activity, such as Pancratistatin (1), 7-Deoxypancratistatin (2), Narciclasine (3), 7-Deoxy-narciclasine (4), trans-Dihydronarciclasine (5) and 7-Deoxy-trans-dihydronarciclasine (6). Nevertheless, preclinical evaluation of these alkaloids has been put on hold due to the limited quantity of materials available from isolation. The current research aimed to explore the underlying cytotoxic molecular mechanisms of the Amaryllidaceae alkaloids (1-6) and to assess their ADMET profiles using chemoinformatic tools. Autodock 4.0 software along with different in silico chemoinformatic tools, namely, PharmMapper, Molinspiration, Metaprint2D and AdmetSAR servers were used to assess the drugability of the Amaryllidaceae alkaloids (1–6). Deoxycytidine kinase (dCK) (PDB: 1P60) was predicted as a potential target with fitting score of 5.574. In silico molecular docking of (1-6) into dCK revealed good interactions, where interesting hydrogen bonds were observed with the amino acid residues GLY-28 and SER-35 located in the highly conserved P-loop motif. This motif plays a special role in dCK function. Contrary to (1), in silico pharmacokinetic results have shown good absorption and permeation and thus good oral bioavailability for (2-6). To conclude, the in silico docking data have proposed that the reported cytotoxic activity of the amaryllidaceae alkaloids (1-6) could be medicated through dCK inhibition. In addition, the ADMET profile of these alkaloids is promising and thus (1-6) could be candidates for future drug development.

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