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Cancer Stem Cells as Potential Targets of Phytotoxic Alkaloids: Drug-likeness Prediction and Molecular Docking Studies

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INTRODUCTION & AIM

In order to permanently arrest the progression of cancers, the cancer stem cells (CSCs) population must be completely eradicated. Targeting these CSCs in anticancer discovery is quite difficult due to the resistance of CSCs to conventional anticancer therapies, low proliferation rate, improved DNA damage repair, and over-expression of anti-apoptotic proteins and multidrug resistance transporters. However, different CSCs targets such as the ABC cassette, surface markers, signal cascade and tumour microenvironment which are involved in the interruption of cell signaling pathways that are critical for the survival and functioning of the CSC population exist. The CSCs is widespread and have now been identified in many different tumors including brain, prostate, melanoma, colon, lung, ovarian and chronic myelogenous leukemia. A number of strategies or pathways for targeting CSCs such as the Notch pathway, Wnt pathway and Hedghog pathway are currently under investigation. Majority of the CSCs targeting therapies involve interruption of cell signaling pathways that are critical for the survival and functioning of the CSC population. The study aims to identify the potential drug-like phytotoxic alkaloids with anticancer activity from the toxic plants-phytotoxins (TPPT) database.

METHOD

A total of 1586 phytotoxins containing 1586 SMILES phytotoxins of potential (eco-)toxicological relevance linked to 844 plant species were filtered to obtain 653 alkaloids. The Lipinski's properties (Log P, molecular weight, and number of hydrogen bond acceptors and donor) and TPSA of the alkaloids were predicted for drug-likeness properties. The toxicity parameters such as hepatotoxicity, carcinogenicity, immunotoxicity, mutgenicity, cytotoxicity and LD_{50}were predicted for the compounds that passed the Lipinski's rule of 5 using ProTox II. Compounds that have no toxicity against the target organs and with high LD_{50} (group 5 or 6 toxicity class) were selected for further analysis. The 3D co-crystallized protein (resolutions < 2.0 Å) complexed with a ligand representing important pathways in cancer stem cell in human beings was obtained from the protein data bank (www.rcsb.org). The target was selected based on the stem cell as potential target for cancer management. The target for docking the 12 drug-like phytotoxic alkaloids is an isomerase perdeuterated E65Q-TIM protein (ID: 7AZA) complexed with phosphoglycolohydroxamate (PGH) ligand, expressed in *E. coli* and resolution of 1.10 Å. The molecular docking adopted blind docking model using the AutoDockTools-1.5.6. The ligands were assigned torsions using the default settings. The potential grid maps were executed using AutoGrid module with 50 hybrid GA-LS runs and population size of 300, 2.5 million energy evaluations and 27000 generations. A root mean square deviation of 2.0 Å was set to group the clusters while other parameters were at default. The docking protocol was validated by re-docking the native ligands into the proteins using the Lamarckian Genetic Search algorithms. The binding poses visualization was performed using Discovery Studio Visualizer v17.2.0.16349 and protein-ligand interaction profiler webserver.

RESULTS & DISCUSSION

The best binding poses were ranked using their binding energies (E) and the inhibition constants (Ki). The evaluation of the protein-ligand best conformational poses identified three alkaloids (norcoclaurine, palustridiene and apovincamine) with Ki < 1.00 µM and E < -9.00 kcal/mol. All the docked ligands bind more efficiently to the isomerase perdeuterated E65Q-TIM protein than the cocrystallized PGH. Significant protein-ligand binding interactions also occurred for (-)-eburnamonine (E = -8.03 kcal/mol; Ki = 1.30 µM) and retamine (E = -7.81 kcal/mol; Ki = 1.89 µM).

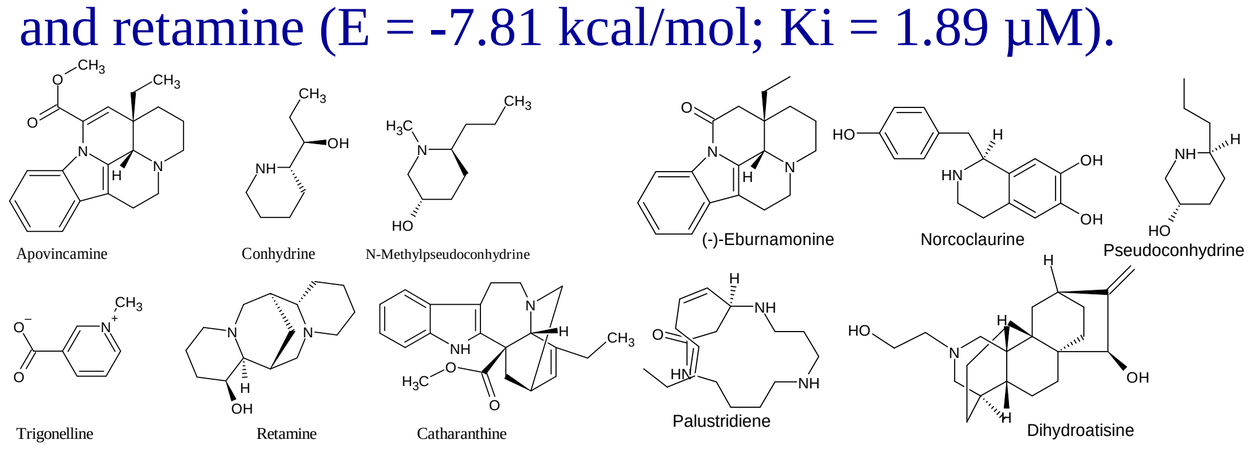

Fig 1. Chemical structure of drug-like phytotoxic alkaloids

Table 1. Drug-likeness properties of alkaloids

Name	Class	a_acc	a_don	logP(o/w)	TPSA	Weight
Norcoclaurine	Isoquinoline	4.00	4.00	2.7380	72.720	271.32
palustridiene	Piperidine	3.00	3.00	1.7950	53.160	293.45
Apovincamine	Indole	2.00	0.00	4.1530	34.47	336.43

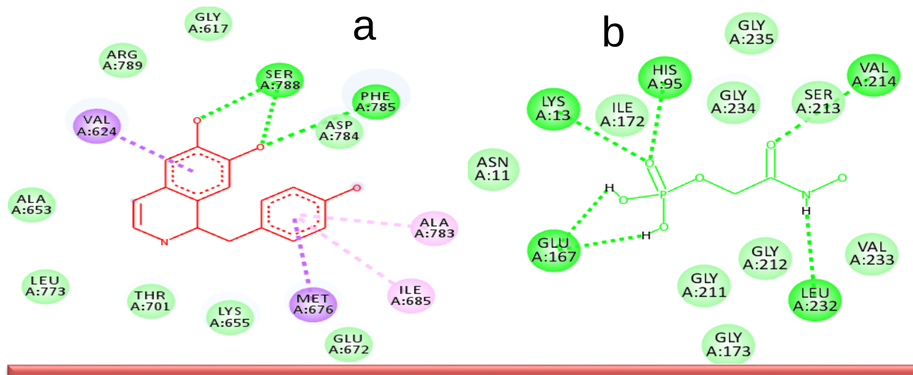

Fig 2. 2D representation of the interactions of (a) apovincamine and (b) palustridiene with 7AZA

CONCLUSION

The efficient inhibition of perdeuterated E65Q-TIM in CSCs by phytotoxic alkaloids provides more insights into understanding the mechanism of anticancer activity of phytotoxic alkaloids.

FUTURE WORK / REFERENCES

Ezema IF *et al*., Exploring Different Drug Targets Responsible for the Inhibitory Activity of N,N′-Substituted Diamine Derivatives in Leishmania. Eng. Proc. 2023, 56, 178. https://doi.org/10.3390/ASEC2023-16264