IN SILICO PREDICTION OF BOERHAAVIA DIFFUSA ROTENOIDS POTENTIAL TO INHIBIT BREAST CANCER RESISTANCE PROTEIN (BCPR)

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INTRODUCTION:

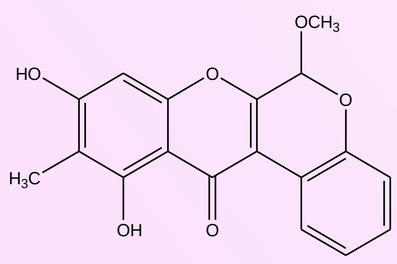
Breast cancer resistance protein (BCRP) is a member of the ATP-binding cassette (ABC) transporter family. BCRP transporter extracts the chemotherapeutics from the tumour cells and thus reduces the therapeutic efficiency of chemotherapeutics. It was found on the membranes of various carcinoma cells including fibrosarcoma, glioblastoma, myeloma, colon breast and gastric carcinoma. Nonprenylated rotenoids from Boerhaavia diffusa (boeravinones and coccineones) were experimentally identified as possible BCRP inhibitors [1]. Their structure has been confirmed by 1H NMR and 13C NMR spectroscopy.

OBJECTIVES:

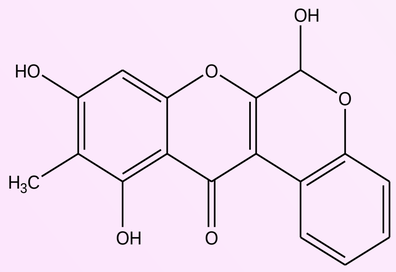
To investigated the interaction profile of thirteen compounds (boeravinones A-J, coccineones B and E, and 6-O-demethylboeravinone H) as BCRP transporter inhibitors.

METHOD / DESIGN:

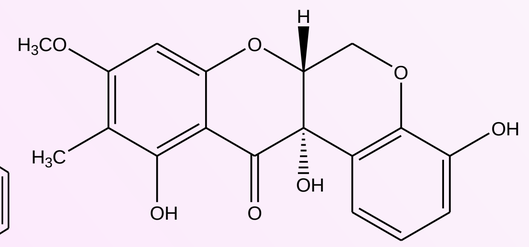
Vienna LiverTox Workspace online tool was applied to investigate the interaction of thirteen rotenoids from B.diffusa with BCRP and to predict whether these molecules inhibit BCRP or not. A score close to 1 indicates a high probability of being an inhibitor while a score close to 0 indicates a high probability of not being an inhibitor. Molecular flatness for the analyzed rotenoids expressed as fraction of sp3 hybridized carbon atoms (Fsp3), polar surface area (PSA) and lipophilicity (XlogP3, WlogP, MlogP) were determined by SwissADME software.



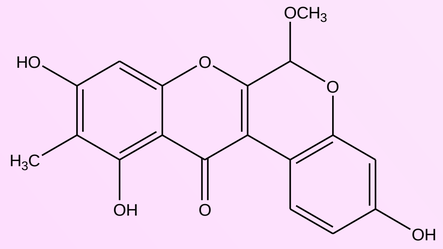
Boeravinone A



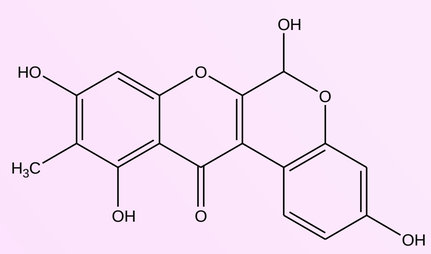
Boeravinone B



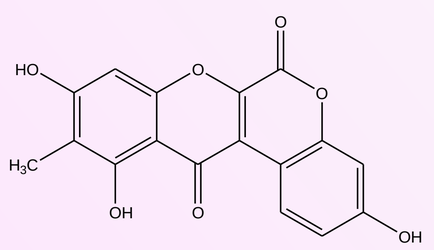
Boeravinone C



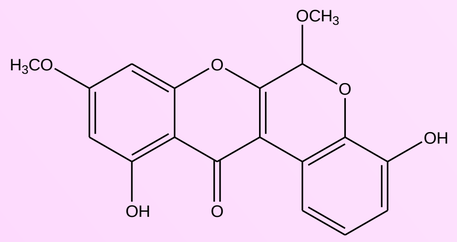
Boeravinone D



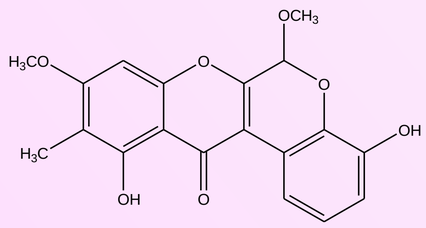
Boeravinone E



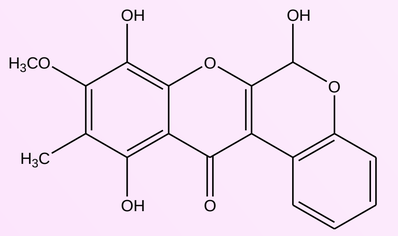
Boeravinone F



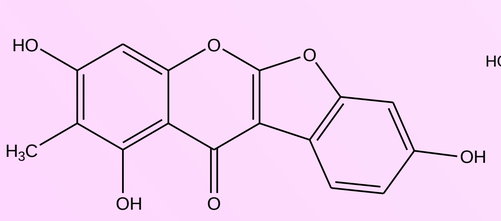
Boeravinone G



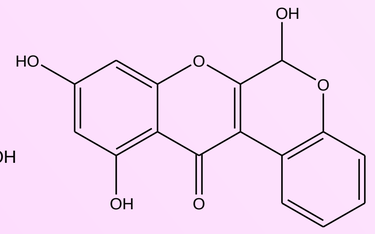
Boeravinone H



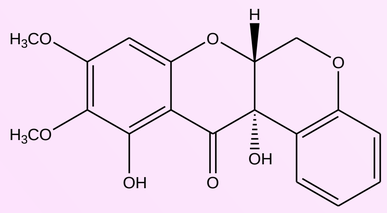
Boeravinone I



Boeravinone J



Coccineone B

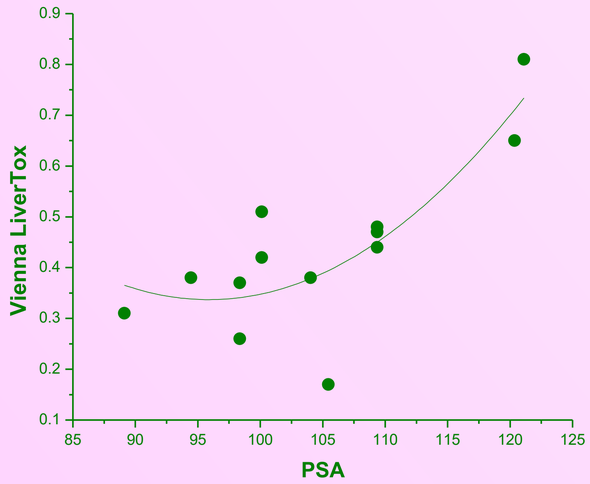


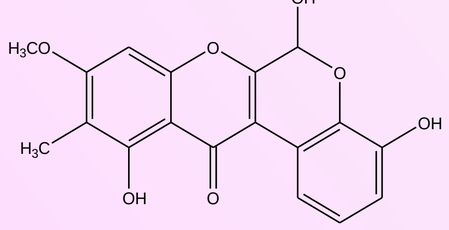
Coccineone E

RESULTS:

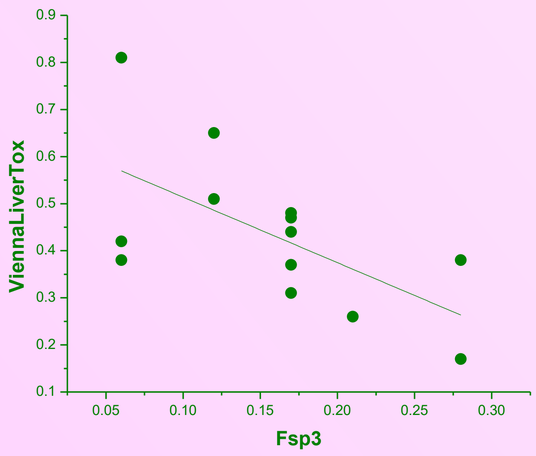
Only boeravinone B, E and F were predicted as BCRP inhibitors by Vienna LiverTox Workspace online tool. However, previously published results indicated that boeravinones A, B, C, E, G, H, I, J, coccineones B and E as well 6-O-demethylboeravinone H are BCPR inhibitors. Experimentally obtained results for BCPR inhibition published previously and *in silico* derived predictions were consistent only for boeravinones B and E. Boeravinone F was predicted to be BCPR inhibitor via Vienna LiverTox Workspace which is inconsistent with experimentally obtained results. Moreover, nine more rotenoids were experimentally proven to accumulate mitoxantrone that was not predicted by the Vienna LiverTox Workspace. Vienna LiverTox Scores for analysed thirteen rotenoids were linearly related with the flatness (Fsp3) of the molecules with statistical significance (r^2=0.334, p=0.023). Also, polarity was correlated with Vienna LiverTox Scores for all observed rotenoids and parabolic function was obtained with high statistical quality (r^2=0.611, p=0.003). However, no association was obtained between Vienna LiverTox Scores and lipophilicity (XlogP3, WlogP or MlogP) of the investigated rotenoids.

Compound	BCRP Inhibition Model		Experimental results [1]	
	BCRP inhibitor	Score	Concentration (μM)	% max accumulation of mitoxantrone
Boeravinone A	–	0.31	10	27±5.1
Boeravinone B	+	0.51	10	55±5.8
Boeravinone C	–	0.17	10	31±4.2
Boeravinone D	–	0.47	n.d	n.d
Boeravinone E	+	0.65	10	56±5.0
Boeravinone F	+	0.81	n.d	n.d
Boeravinone G	–	0.37	5	92±6.5
Boeravinone H	–	0.26	5	68±6.1
Boeravinone I	–	0.48	20	12±5.4
Boeravinone J	–	0.38	20	15±3.1
Coccineone B	–	0.42	10	29±5.3
Coccineone E	–	0.38	10	15±5.2
6-O-demethylboeravinone H	–	0.44	20	15±3.1





6-O-demethylboeravinone H



CONCLUSIONS:

Based on the obtained results rotenoinds extracted from B.diffusa should be considered as potential BCPR inhibitors. Further studies involving the proper in silico strategy applied with complement experiments could enable the development of deep learning algorithms and independent validation datasets that would select promising rotenoid with favourable biological potential. Computational modelling reduces the time and the cost involved in drug discovery process. The combination of computer-aided drug development with good designed experiments allows understanding of the complex interrelation between molecular properties of a compound and its biological effect, which cannot be accomplished by single approach.

Reference:
[1] Ahmed-Belkacem A, Macalou S, Borrelli F, Capasso R, Fattorusso E, Taglialatela-Scafati O, Di Pietro A. Nonprenylated rotenoids, a new class of potent breast cancer resistance protein inhibitors. J Med Chem. 2007;50(8):1933-8. doi: 10.1021/jm061450q.