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PREDICTION OF ECOTOXICITY AND PHARMACOKINETICS OF SELECTED PHYTOCHEMICALS OF AREAL PARTS OF *Heliotropium indicum* LINNAEUS AND SYNTHETIC DRUGS

Bioinformatics

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ABSTRACT

It was attempted an in silico prediction towards ecotoxicity and pharmacokinetics properties of selected phytochemicals of H. indicum compared to synthetic drugs. The ecotoxicity predictions for algae, daphnids and fish were carried out by using two different tools, viz. "ECOSAR" (version, 1.11) and "T.E.S.T" (version, 1.11). Moreover, pharmacokinetics prediction by using Swiss-ADME online tool was also performed. The lower EC50 (mg/L) values for phytochemicals viz. β-Linalool (5.929) and Lasiocarpine (2.599) similar to Indomethacin (3.573) on algae. The lower LC50 (mg/L) values for phytochemicals viz. Heliotridine (0.818) and β-Linalool (4.710) as like Indomethacin (7.340) and Ibuprofen (2.800) on daphnids. The lower LC50 (mg/L) values for phytochemicals viz. Lasiocarpine (4.380), Indicine N-oxide (4.755), Heliotridine (7.258) and Supinine (9.070) as drugs like Indomethacin (0.320) and Ibuprofen (5.490) on fish. All compounds were <500 gms/mol. All compounds were obtained higher GI absorption while BBB absorption was obtained for Heleurine and β-Linalool like synthetic drugs. The majority of compounds were P-glycoprotein substrate negative except 4 phytocompounds. For inhibitory activity on cytochrome p450 isomers viz. CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 were obtained positive for former three related to Indomethacin. All compounds were soluble except 1 phytocompound as moderately soluble. In conclusion, this in silico prediction of different phytocompounds of H. indicum and synthetic drugs obtained the drug-like properties as per solubility, molecular weight, H-bond acceptor and donor values. Future study should be performed the molecular docking and interaction along with molecular dynamics study in future for identifying small lead molecule(s) for new drug design.

KEYWORDS

Drug-like Properties, Ecotoxicity, H. Indicum, In Silico, Pharmacokinetics, Phyto And Synthetic Compounds

INTRODUCTION

The study is based on chemicals interaction with living organisms in their environment, is known as ecotoxicology and the mechanism within the body is called ecological toxicity or ecotoxicity. The variety of potentially hazardous environments is vast, encompassing terrestrial environments from the arctic to the tropics, marine and freshwater environments, and even the atmosphere, where plants may absorb pollutants through their leaves and people may inhale them. Chemical exposures can harm a variety of organisms, including plants, fungi, and algae (primary producers); invertebrates like worms, bugs, beetles, and mollusks; fish; amphibians; reptiles; birds; and mammals.[1] As per many reports, one of the drivers of biodiversity damage at the local and regional levels is ecotoxicological stress caused by chemical discharges, which is also a known global concern.[2-7]

Besides ecotoxicity studies, pharmacokinetics is an important research arena in which investigators could recognize drug-like products. Last few decades, natural products are mostly emphasized in new drug discovery.[8] In this context, *in silico* prediction of pharmacokinetics especially physico-chemical properties, absorption, distribution, metabolism, excretion (ADME) profiling, bioavailability and drug-likeness lead to faster screening, without animal harming and no wet lab cost.[9,10]

In past studies, many investigators reported the therapeutic efficacy of weed (*Heliotropium indicum* Linnaeus) for medicinal usage traditionally.[11-15] In the present study, an *in silico* prediction was performed for ecotoxicity and pharmacokinetics properties of selected phytochemicals of *H. indicum* compared to synthetic drugs.

MATERIALS AND METHODS

As per our earlier study, the similar phytochemicals of *H. indicum* and synthetic drugs were selected.[16] Table 1 exhibited the "CAS registry number and SMILES notation" for each phytoconstituent and synthetic drugs.

The ecotoxicity predictions for algae, daphnids and fish were carried out by using two different tools, viz. "Ecological Structural Activity Relationships or ECOSAR" (version, 1.11)[17] and "Toxicity Estimation Software Tool or T.E.S.T" (version, 1.11)[18]

Next part of the work was performed pharmacokinetics based on physico-chemical properties, and ADME profiling by using Swiss-ADME online tool as per the previous studies.[19,20] A BOILED-EGG representation was retrieved from this tool as per inbuilt development.[21]

Table 1: CAS and SMILES of phytochemicals of areal parts of *H. indicum* and synthetic medicines

Sl. No.	Compounds name	CAS registry No.	SMILES notation
Phytochemicals			
1.	Heleurine	488-00-6	C[C@H]([C@@](C(C)C)(C(=O)OCC1=CCN2[C@H]1CCC2)O)OC
2.	Echinatine	480-83-1	C[C@@H]([C@@](C(C)C)(C(=O)OCC1=CCN2[C@H]1[C@H](CC2)O)O)O
3.	Heliotrine	303-33-3	C[C@H]([C@@](C(C)C)(C(=O)OCC1=CCN2[C@H]1[C@H](CC2)O)O)OC
4.	Heliotridine	520-63-8	C1CN2CC=C([C@@H]2[C@H]1O)CO
5.	Indicine	480-82-0	C[C@@H]([C@](C(C)C)(C(=O)OCC1=CCN2[C@H]1[C@@H](CC2)O)O)O
6.	Indicine N-oxide	41708-76-3	C[C@@H]([C@](C(C)C)(C(=O)OCC1=CC[N+]2([C@H]1[C@@H](CC2)O)[O-])O)O
7.	Lasiocarpine	303-34-4	C/C=C(/C)\C(=O)O[C@H]1CCN2[C@@H]1C(=CC2)COC(=O)[C@@]([C@H](C)OC)(C(C)(C)O)O
8.	Trachelanthamidine	526-64-7	C1C[C@H]2[C@@H](CCN2C1)CO
9.	Retronecine	480-85-3	C1CN2CC=C([C@@H]2[C@@H]1O)CO
10.	Supinine	551-58-6	C[C@H]([C@@](C(C)C)(C(=O)OCC1=CCN2[C@H]1CCC2)O)O
11.	β-Linalool	78-70-6	CC(=CCCC(C)(C=C)O)C
Synthetic medicines			
1.	Indomethacin	53-86-1	CC1=C(C2=C(N1C(=O)C3=CC=C(C=C3)Cl)C=CC(=C2)OC)CC(=O)O
2.	Ibuprofen	15687-27-1	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O

CAS = Chemical abstract service; SMILES = Simplified Molecular Input Line Entry System

RESULTS

Table 2 predicts the results of ecotoxicity of phytochemicals of areal parts of *H. indicum* and synthetic drugs. The lower EC_{50} values for phytochemicals viz. β-Linalool (5.929 mg/L) and Lasiocarpine (2.599 mg/L) while for synthetic drugs like Indomethacin (3.573 mg/L) on algae. The lower LC_{50} values for phytochemicals viz. Heliotridine (0.818 mg/L) and β-Linalool (4.710 mg/L) while for synthetic drugs like Indomethacin (7.340 mg/L) and Ibuprofen (2.800 mg/L) on daphnids. The lower LC_{50} values for phytochemicals viz. Lasiocarpine (4.380 mg/L), Indicine N-oxide (4.755 mg/L), Heliotridine (7.258 mg/L), Supinine (9.070 mg/L) and β-Linalool (11.820 mg/L) while for synthetic drugs like Indomethacin (0.320 mg/L) and Ibuprofen (5.490 mg/L) on fish.

Table 2: Prediction of ecotoxicity of phytochemicals of areal parts of *H. indicum* and synthetic drugs

Sl. No.	Compounds name	Algae EC_{50} value (mg/L)	Daphnids LC_{50} value (mg/L)	Fish LC_{50} value (mg/L)
Phytochemicals				
1.	Heleurine	213.499	16.290	23.670
2.	Echinatine	587.738	1194.608	2325.917
3.	Heliotrine	1366.643	34.180	37.710
4.	Heliotridine	3188.683	0.818	7.258
5.	Indicine	587.738	54.090	16.650
6.	Indicine N-oxide	27.011	85.375	4.755
7.	Lasiocarpine	2.599	13.740	4.380
8.	Trachelanthamidine	416.926	934.427	1862.858
9.	Retronecine	188.521	158.640	400.040
10.	Supinine	47.920	41.220	9.070
11.	β-Linalool	5.929	4.710	11.820
Synthetic medicines				
1.	Indomethacin	3.573	7.340	0.320
2.	Ibuprofen	15.574	2.800	5.490

Table 3 predicts the results of physico-chemical properties of phytochemicals of areal parts of *H. indicum* and synthetic drugs in which all compounds were <500 gms/mol.

Table 3: Prediction of physico-chemical properties of phytochemicals of areal parts of *H. indicum* and synthetic drugs

Sl. No.	Compounds name	GI absorption	BBB permeant	Pgp substrate	CYP 1A2 inhibitor	CYP 2C19 inhibitor	CYP2 C9 inhibitor	CYP2 D6 inhibitor	CYP 3A4 inhibitor
Phytochemicals									
1.	Heleurine	High	Yes	No	No	No	No	No	No
2.	Echinatine	High	No	Yes	No	No	No	No	No
3.	Heliotrine	High	No	No	No	No	No	No	No
4.	Heliotridine	High	No	No	No	No	No	No	No
5.	Indicine	High	No	Yes	No	No	No	No	No
6.	Indicine N-oxide	High	No	Yes	No	No	No	No	No
7.	Lasiocarpine	High	No	Yes	No	No	No	No	No
8.	Trachelanthamidine	High	No	No	No	No	No	No	No
9.	Retronecine	High	No	No	No	No	No	No	No
10.	Supinine	High	No	No	No	No	No	No	No
11.	β-Linalool	High	Yes	No	No	No	No	No	No
Synthetic medicines									
1.	Indomethacin	High	Yes	No	Yes	Yes	Yes	No	No
2.	Ibuprofen	High	Yes	No	No	No	No	No	No

Table 4 predicts the absorption and metabolism profiling of phytochemicals of areal parts of *H. indicum* and synthetic drugs in which all compounds were obtained higher GI absorption while BBB absorption was obtained for Heleurine and β-Linalool like synthetic drugs. The majority of compounds were Pgp substrate negative except 4 phytocompounds. For inhibitory activity on cytochrome p450 isomers viz. CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 were obtained positive for former three related to Indomethacin. The BOILED-EGG is depicted in Fig 1.

Table 4: Prediction of Absorption and metabolism profiling of phytochemicals of areal parts of *H. indicum* and synthetic drugs

Sl. No.	Compounds name	MW (gms/mol)	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp3
Phytochemicals					
1.	Heleurine	297.39	21	0	0.81
2.	Echinatine	299.36	21	0	0.80
3.	Heliotrine	313.39	22	0	0.81
4.	Heliotridine	155.19	11	0	0.75
5.	Indicine	299.36	21	0	0.80
6.	Indicine N-oxide	315.36	22	0	0.80
7.	Lasiocarpine	411.49	29	0	0.71
8.	Trachelanthamidine	141.21	10	0	1.00
9.	Retronecine	155.19	11	0	0.75
10.	Supinine	283.36	20	0	0.80
11.	β-Linalool	154.25	11	0	0.60
Synthetic medicines					
1.	Indomethacin	357.79	25	15	0.16
2.	Ibuprofen	206.28	15	6	0.46
		#Rotatable bonds	**#H-bond acceptors**	**#H-bond donors**	**MR**
Phytochemicals					
1.	Heleurine	7	5	1	84.70
2.	Echinatine	6	6	3	81.14
3.	Heliotrine	7	6	2	85.87
4.	Heliotridine	1	3	2	45.00
5.	Indicine	6	6	3	81.14
6.	Indicine N-oxide	6	6	3	84.50
7.	Lasiocarpine	10	8	2	110.7
8.	Trachelanthamidine	1	2	1	44.31
9.	Retronecine	1	3	2	45.00
10.	Supinine	6	5	2	79.97
11.	β-Linalool	4	1	1	50.44
Synthetic medicines					
1.	Indomethacin	5	4	1	96.12
2.	Ibuprofen	4	2	1	62.18

Table 4 predicts the lipophilicity and solubility of phytochemicals of areal parts of *H. indicum* and synthetic drugs. For lipophilicity, iLOGP, XLOGP3, WLOGP and MLOGP values with a range between 1.11 to 3.01, -1.29 to 4.27, -1.03 to 3.93 and -1.76 to 3.30, respectively were recorded. For solubility, all compounds were soluble except 1 phytocompound as moderately soluble.

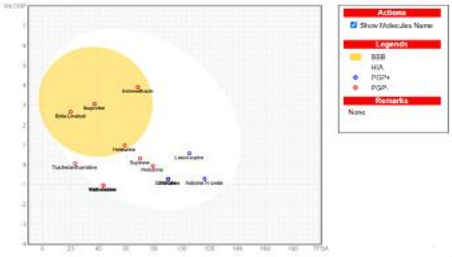

Fig 1: BOILED-EGG representation for absorption pattern

Table 4: Prediction of lipophilicity and solubility of phytochemicals of areal parts of *H. indicum* and synthetic drugs

Sl.	Compounds name	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Solubility (mg/ml)	Silicos-IT class
Phytochemicals							
1.	Heleurine	3.01	1.08	0.98	1.13	1.74	Soluble
2.	Echinatine	2.53	-0.44	-0.71	0.07	0.32	Soluble
3.	Heliotrine	2.81	0.91	-0.05	0.32	0.86	Soluble
4.	Heliotridine	1.36	-1.29	-1.03	-0.12	-0.06	Soluble
5.	Indicine	3.54	-0.44	-0.71	0.07	0.32	Soluble
6.	Indicine N-oxide	1.11	-0.91	-0.70	-1.76	-3.02	Soluble
7.	Lasiocarpine	3.43	1.28	0.58	0.52	1.56	Soluble
8.	Trachelanthamidine	1.88	0.52	0.08	0.90	0.89	Soluble
9.	Retronecine	1.45	-1.29	-1.03	-0.12	-0.06	Soluble
10.	Supinine	2.70	0.54	0.32	0.88	1.19	Soluble
11.	β-Linalool	2.70	2.97	2.67	2.59	2.35	Soluble
Synthetic medicines							
1.	Indomethacin	2.76	4.27	3.93	3.30	3.91	Moderately
2.	Ibuprofen	2.17	3.50	3.07	3.13	3.15	Soluble

DISCUSSION

In the recent *in silico* study, the ecotoxicity predictions for algae, daphnids and fish were the first-time endeavour. No past studies were recorded for food chain based ecotoxicity assessment with these phytocompounds.

Generally, Swiss-ADME online tool was used to analyze the drug-likeness and ADME of the compounds. The efficacy of all the chemicals was assessed using a variety of variables, including rotatable bonds (which reflect flexibility), solubility and hydrophobicity (Log S), carbon fraction sp3 (measurement of saturation carbons in hybridization with sp3), cytochrome P450 inhibitor isoenzymes, P-glycoprotein (PGP), human intestinal absorption (HIA), blood-brain barrier (BBB), and the Lipinski rule. Lipinski's "rule of 5" and the amount of free rotatable bonds were examined to see if the selected compounds had any drug-like characteristics. have fewer than five hydrogen donors. According to the rule of five, a molecule is considered to be drug-like if it meets at least two of the following criteria: Its molecular weight must be <500 Daltons, its lipophilicity (Log P) must be below 5, it must have <five hydrogen donors, and its number of hydrogen bond acceptors must be below ten.[22]

As per past study by Afroz Shoily et al.,[23] a similar finding was obtained in this study that the majority of phytocompounds were closely related to the synthetic drugs and could be the drug-like capability regarding solubility, molecular weight, H-bond acceptor and donor along with bioavailability radar.

CONCLUSION

It is concluded that the *in silico* prediction of different phytocompounds of *H. indicum* and synthetic drugs like Indomethacin and Ibuprofen obtained the drug-like properties as per solubility, molecular weight, H-bond acceptor and donor values. It is suggested to perform the molecular docking and interaction along with molecular dynamics study in future for identifying small lead molecule(s) for new drug design.

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Conflict of interest

It is declared none.

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