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Evaluation of drug-likeness properties and pharmacological potential of Bioactive Constituents from *Veratrum dahuricum* by Chemoinformatic and pharmacoinformatic approach

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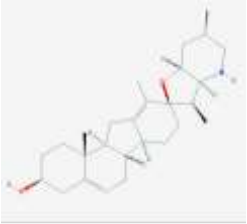
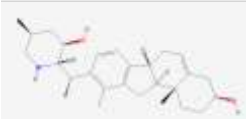
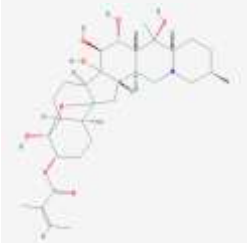
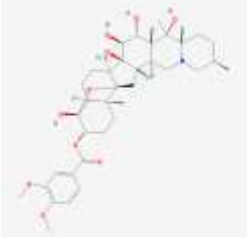
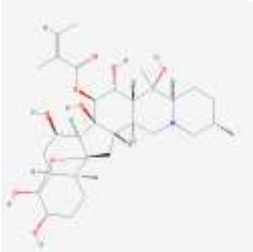
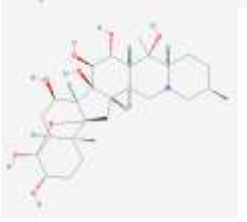
Plants are being widely used for centuries, either as a single drug or in combination in health care delivery system. Ethnobotanicals can be importantan source of previously unknown chemical constituents with potential therapeutic values. The pharmacological activities and mechanisms of action of these plant-derived compounds are now a major area of investigation. Using conventional approaches for the drug discovery to select the best single or group of best phytochemical for studying the effectiveness in treating or preventing disease is extremely time consuming and cost effective. However *in silico* methodology provides a novel approach to guide the early stages of hypothesis development and experimental design that has the potential to create subsequent efficiencies and cost savings in the laboratories. The present investigation deals with virtual screening of *Veratrum dahuricum* phytocompounds for their pharmacological potential and biological activities. The dataset comprising of compounds isolated from *Veratrum dahuricum* were used for virtual screening by employing various pharmacoinformatics tools. The result indicated that all the ten compounds analyzed were non mutagens, non-carcinogens and having good bioactivity scores and drug-likeness properties. The ADMET profiles were analyzed by admetSAR online server and results shows the ADMET in satisfying ranges. Pharmacological activities of these compounds were predicted individually using PASS server many different pharmacological activities and mechanisms of action shown by these compounds were reported. Hence, ADMET descriptor, pharmacophore, and three-dimensional quantitative structure–activity relationship (3D-QSAR) studies, the compounds was suggested to be promising therapeutics that have higher odds of not being discarded in the clinical phase.

KEYWORDS: *Veratrum dahuricum*, phytopharmaceuticals, ADMET, PASS, *pharmacoinformatics*, pharmacokinetics, *in silico.*

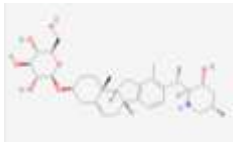
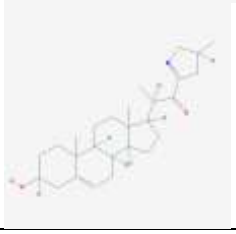
INTRODUCTION

The use of plants and plant based products as medicine is as old as human civilization. Human beings use plants to cure various ailments and to get relief from physical sufferings in both developing and least developed countries (Muniyandi and Jayachitra, 2015). Most of the developing countries such as China, India, Sri Lanka and a few others blessed with vast resources of ethnomedicinal plants (suhail*et al*., 2016). India is one of the largest producers of herbs and herbal products (Garaniya and Bapodra, 2014). Thousands secondary plant metabolites generates polyphenolic compounds via phenylpropanoid metabolic pathways (Kretzschmar*et al*. 2007). Plants being rich sources of polyphenols such as alkaloids, terpenoids, triterpenies, flavanoids, tannins, and phenolic compounds etc. which are responsible for various biological activities have been used as treatment for various ailments (de-Fathima*et al*., 2006). The National Cancer Institute (NCI) alone has reportedly screened more than 120,000 plant extracts from 35,000 species for isolation and characterization of novel anticancer phytocompounds (Sateesh *et al*., 2014). The use of Ethnobotanicals for the primary healthcare has gained considerable importance in recent years in both developed as well as developing countries because of their wide biological, higher safety margins, lesser costs and As more people

Table 1: 2D and 3D structures of Alkaloids Isolated from *Veratrum dahuricum*

Sl no	Compound	Pubchem CID number	2D structure	3D Structure
1	cyclopamine	442972		
2	veratramine	6070		
3	jervine	10098		
4	3-angeloylzygadenine	6441115		
5	3-veratroylzygadenine	6419927		
6	15-angeloylgermine	100937115		
7	germine	442976		

Continuation of table one

8	veratrosine	23616879		
9	pseudojevine	16398499		
10	Tomatillidine	255353		

Become aware of the tendency and side effects of synthetic drugs (WHO Report, 2002; Chaudhary *et al*., 2010; Long *et al*., 2014). Through the exploration of ethnopharmacology and traditional medicine many drugs have entered the international market (Higgins *et al*., 2012). However by conventional method of drug discovery for treating or preventing disease is highly challenging, time consuming and cost effective (Dong *et al*., 2012). Instead of testing each compound in a large compound library experimentally by using high-throughput screening (HTS), virtual screening tools can be used to select compounds on their probability of binding to the target. This leads to considerable savings in personnel and material costs as only a small number of molecules of the complete library need to be tested experimentally (Trisilowati & Mallet, 2012). Virtual screening plays a central role in drug discovery in the present era. Many molecules can be tested in silico with the aim of selecting the most promising ones and testing them experimentally which allow researchers to refine their experimental programs to reduce costs and increase research efficiency (Asma, 2015). Hence, the present study aims to investigate the therapeutic properties and pharmacological potentials of the isolated alklaloids from *Veratrum*dahuricum by in silico approach using various improved generation Chemoinformatic and pharmacoinformatic tools. The selection of plant for screening was based on their ethnobotanical uses as well as reported anticancer properties in the literature. The genus *Veratrum*is an important genus of Liliaceae family, with more than 40 species, this plant is used to treat several diseases in China such as apoplexy, epilepsy, phlegm, hypertension, blood stroke etc., (Cong *et al*., 2015) The crude extract, total alkaloids and some steroidal compounds from *Veratrum*plants showed significant antitumor effect and inhibit the proliferation of human bladder cancer T24 cells (Zhang *et al*., 2009; Chen *et al*., 2001; Xuetao *et al*., 2015).

METHODS AND IMPLEMENTATION

In silico analysis of *pharmacokinetics* profiles

Preparation of ligands

The ten alkaloids isolated from *Veratrum*dahuricum viz., “cyclopamine, veratramine, jervine, 3, 15-diangyloylgermine, 3-angyloylzygadenine, 3-veratroyl zygadenine, 15-veratroylgermine, germine, veratrosine, pseudojervine (Zhang *et al*., 2009) and Tomatillidine (cong *et al*., 2015)” were analyzed for their pharmacokinetics i.e., ADMET analysis,

Pharmacological Potential and biological activity for use as promising phytodrugs. The 2D and 3D structures of these isolated compounds were retrieved from online databases; PubChem (http://pubchem.ncbi.nlm.nih.gov/) and each chemical compound was drawn using ACD/ Chemsketch software and saved in the '.mol' format (Suhail *et al*., 2016; Riju *et al*., 2009).Table 1: 2D and 3D structures of Alkaloids Isolated from *Veratrumdahuricum*

Computation of pharmacokinetics profiles and biological activity

The ten compounds were analyzed individually for their pharmacological potential and biological activities. The "drug-likeness" properties of the compounds were carried out with Lipinski's ro5 "Rule of Five", (Lipinski, 2004) using MolSoft online tool, and the pharmacokinetic profiles such as Absorption, Distribution, Metabolism, Excretion and the Toxicity of the phytochemicals is evaluated using admetSAR (http:// www.admetexp.org) online server which provides the latest and most comprehensive manually curated data for diverse chemicals associated with known ADMET profiles (Paramashivam *et al*., 2015; Polachi *et al*., 2015).Using Molinspiration online server bioactivity scores for the most important pharmacophore drug targets such as GPCR ligand, Ion channel modulator , Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor, Protease inhibitor and Enzyme inhibitor were predicted (sateesh *et al* 2016; Balasundaram *et al*., 2016). PASS (Prediction of activity spectra for substances) is an online computational server employed for prediction of pharmacological activities and mechanism of actions based on structural activity relationship (SAR) (Suhail *et al* 2016).

RESULT AND DISCUSSION

Assessment of Drug-Likeness properties

The drug-likeness properties of the phytochemicals was predicted using molsoft online server based on the 'rule-of-five' given by Lipinski, the rule states that most "druglike" molecules must have log P≤ 5 (partition coefficient) , molecular weight ≤ 500, number of hydrogen bond acceptors(HBA) ≤ 10, and number of hydrogen bond donors(HBD) ≤ 5. Molecules violating more than one of these rules may have problems with oral bioavailability (Sateesh *et al* 2016). By investigation it was pleasant to see most of alkaloids significantly following the Lipinski's RO5 and having good oral bioavailability (table 2) with good Drug-likeness model score (fig 1-fig 10) which shows that these compounds are potential phytopharmaceuticals.

Table 2 Prediction of Lipinski's rule of five and Drug-likeness properties using Molsoft.

Compound	Molecular Formula	Molecular Weight ≤ 500	Hydrogen Bond accepter (HBA) ≤ 10	Hydrogen Bond Donator (HBD) ≤ 5	Mol LogP P≤ 5	TPSA	Drug-likeness model score
1	C27 H41 N O2	411.31	3	2	5.13	41.49	0.00
2	C27 H39 N O2	409.30	3	3	4.68	52.48	0.52
3	C27 H39 N O3	425.29	4	2	4.22	58.56	0.07
4	C32 H49 N O8	575.35	9	5	2.15	139.92	0.66
5	C36 H51N O10	657.35	11	5	2.53	158.38	1.19
6	C32 H49 N O9	591.34	10	6	1.11	160.15	1.07
7	C27 H43 N O8	509.30	7	9	-0.67	154.07	0.49
8	C33 H49 N O7	571.35	8	6	2.33	131.63	0.49
9	C33 H49 N O8	587.35	9	5	1.87	137.71	0.55
10	C27 H41 N O2	411.31	3	1	5.55	49.66	0.74

Prediction of bioactivity score

Molinspiration tool (www.molinspiration.com) was used to predict bioactivity scores for the most essential drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors) and the Drug likeliness property of ten compounds against these targets were depicted in table 3. The compound having bioactivity score more than 0.00 is likely to possess considerable biological activities, values -0.50 to 0.00 are expected to be moderately active

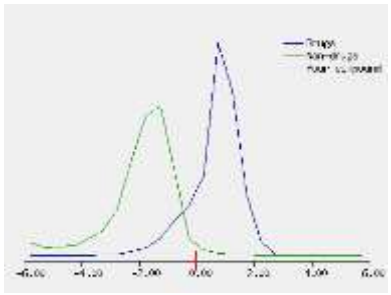


Fig 1. Drug-likeness model score: -0.00

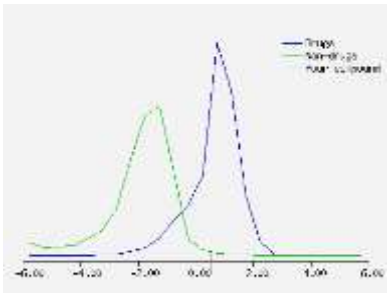


Fig 2. Drug-likeness model score: 0.52

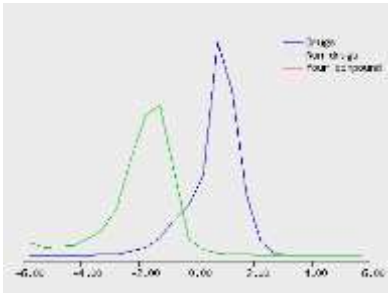


Fig 3. Drug-likeness model score: 0.07

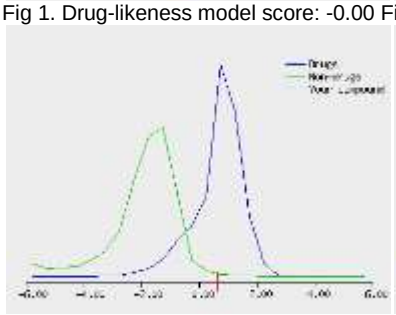


Fig4. Drug-likeness model score: 0.66

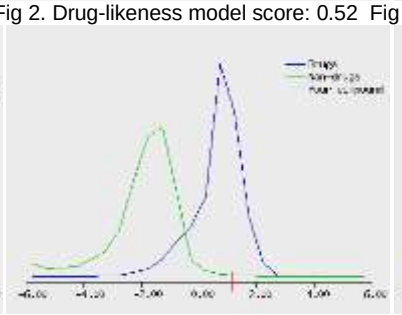


Fig 5. Drug-likeness model score: 1.19

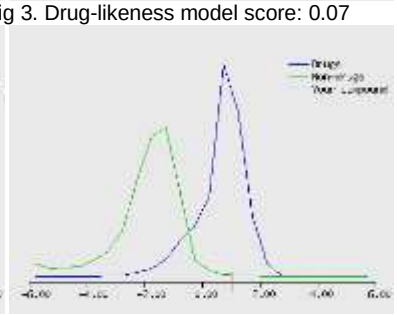


Fig 6. Drug-likeness model score: 1.07

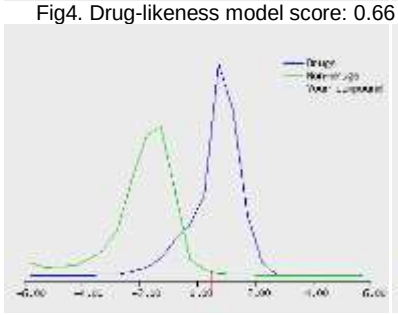


Fig 7. Drug-likeness model score: 0.49

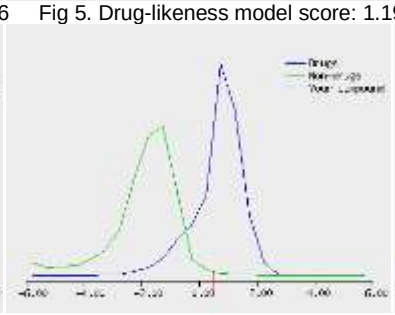


Fig 8. Drug-likeness model score: 0.49

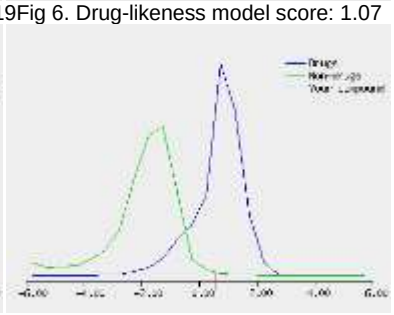


Fig 9. Drug-likeness model score: 0.55

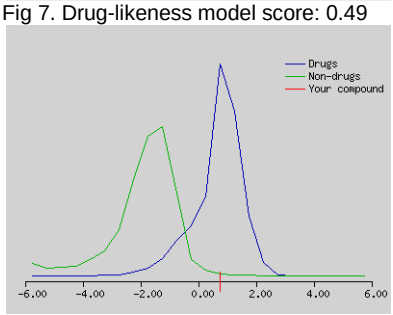


Fig 10. Drug-likeness model score: 0.74

Table 3 prediction of bioactivity scores of Phytocompounds by Molinspiration.

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	0.09	-0.12	-0.49	0.36	0.12	0.63
2	0.50	0.09	-0.34	0.46	0.39	0.47
3	0.03	-0.25	-0.53	0.34	0.13	0.58
4	0.09	-0.18	-0.40	0.27	0.08	0.28
5	-0.29	-0.94	-0.81	-0.47	-0.11	-0.39
6	0.11	-0.19	-0.44	0.22	0.13	0.29
7	0.22	0.17	-0.15	0.37	0.28	0.44
8	0.42	-0.18	-0.34	0.13	0.34	0.38

Continuation of table 3

9	**0.05**	**-0.51**	**-0.54**	**-0.01**	**0.15**	**0.41**
10	0.08	0.01	-0.51	0.60	0.01	0.49

And if score is less than -0.50, it is presumed to be inactive (Suhail*et al*., 2016; Paramashivam *et al*., 2015). Hence from the evaluated scores one can say that all the compounds having bioactivity score in acceptable ranges.

ADME/T analysis

The knowledge of pharmacokinetics and pharmacodynamics of compounds is very essential in order to provide safe and effective drug therapy. Since most of the compounds fails to enter the market as they have poor ADME profiles and high range of toxicity (Ntie-Kang, 2013). In view of these, computer-based methods like ADMET tool play a vital role in the studies of molecular descriptors and drug-likeness properties (Polachi *et al*., 2015; Lombardo *et al*., 2003). The various parameters such as blood brain barrier, Caco-2 cell permeability, Human intestinal absorption, P-gp substrate, P-gp inhibitor, Ames mutagenicityand carcinogenicity were analyzed through computational methods by employing AdmetSAR tool, this database is having 22 qualitative classification and 5 quantitative regression models with highly predictive accuracy, used to estimate mammalian ADMET properties for novel compounds (Balakin *et al*., 2005). The predicted values of ADMET parameters were reported in table 4 and it was fortunate to see that all the compounds predicted to be having very good ADMET profiles with neither toxic nor mutagenic in nature.

a-Predicted blood/brain barrier partition coefficient (concern value is −3.0 to 1.0) , b-predicted Caco-2 cell permeability in nm/s (acceptable range: −1 is poor, 1 is great), c-predicted human intestinal absorption in nm/s (acceptable range: 0 poor, >1 great), d-predicted P-gp substrate in nm/s (acceptable range of −5 is poor, 1 is great), e-predicted P-glycoprotein inhibitor in nm/s (accepted range: 0-1), f-predicted aqueous solubility, (concern value is −6.5 to –0.5). P-gp: P-glycoprotein, HIA: Human intestinal absorption, ADME: Absorption, distribution, metabolism, excretion NT: Non Ames toxic, NC: non carcinogens.

Table 4 ADME/TOX and evaluation of pharmacological parameter of phytocompounds predicted using admetSAR toolbox.

Compond	PlogBB[a]	$\log_{HIA}$[c]	PCaco[b]	logpGI (substrate)[d]	logpGI (non-inhibitor)[e]	PlogS[f]	AMES Toxicity	Carcin-ogens
1	0.9670	1.0000	0.5450	0.7655	0.6076	-4.1047	NT	NC
2	0.9555	1.0000	0.5757	0.8640	0.6832	-4.1347	NT	NC
3	0.9284	1.0000	0.5211	0.8129	0.6621	-3.9988	NT	NC
4	0.6908	0.7811	0.5847	0.9283	0.7792	-2.4608	NT	NC
5	0.6734	0.6057	0.5395	0.9252	0.6130	-2.3647	NT	NC
6	0.6869	0.8143	0.6056	0.9395	0.7769	-2.5744	NT	NC
7	0.6156	0.7237	0.5432	0.8869	0.5276	-2.4986	NT	NC
8	0.7819	0.7380	0.7541	0.9124	0.5248	-3.8995	NT	NC
9	0.5531	0.7770	0.7763	0.8525	0.5120	-3.2227	NT	NC
10	0.9746	1.0000	0.6048	0.7717	0.6891	-3.5947	NT	NC

[a]-Predicted blood/brain barrier partition coefficient (concern value is −3.0 to 1.0) , [b]-predicted Caco-2 cell permeability in nm/s (acceptable range: −1 is poor, 1 is great), [c]-predicted human intestinal absorption in nm/s (acceptable range: 0 poor, >1 great), [d]-predicted P-gp substrate in nm/s (acceptable range of −5 is poor, 1 is great), [e]-predicted P-glycoprotein inhibitor in nm/s (accepted range: 0-1), [f]-predicted aqueous solubility, (concern value is −6.5 to –0.5). P-gp: P-glycoprotein, HIA: Human intestinal absorption, ADME: Absorption, distribution, metabolism, excretion NT: Non Ames toxic, NC: non carcinogens.

Prediction of pharmacological potential

The biological activities and the mechanisms of actions of the ten compounds was predicted with the help of PASS (Prediction of activity spectra for substances) computer program (http://www.way2drug.com/PASSonline/) (Jamkhande *et al*., 2014) and the various probable mechanisms of actions and biological activities such as Membrane permeability enhancer, Chloride channel blocker, Gestagen antagonist, Phosphatase inhibitor, Chemopreventive, Antibacterial, Hepatoprotectant, Antithrombotic, Protein synthesis inhibitor, Antiinflammatory etc., shown by these compounds were reported in table 5. The program Prediction of this spectrum by PASS is based on structural activity relationship (SAR) analysis of the training set containing more than 205,000 compounds exhibiting more than 3750 kinds of biological activities (Suhail *et al*., 2016). The predicted activity spectrum of a compound is estimates as probable activity (Pa) and Probable inactivity (Pi) the values of Pa and Pi vary between 0.000 and 1.000. Only activities with Pa > Pi are considered as possible for a particular compound. If Pa > 0.7, the probability of experimental pharmacological action is

high and if 0.5 < Pa < 0.7, probability of experimental pharmacological action is less (sateesh *et al*., 2016; Goel*et al*., 2011).

Table 5: Predicted biological activities and mechanism of actions with Pa and Pi values of phytocompounds using PASS.

Sl no	Pa	Pi	Biological activities and mechanisms of action	pa	Pi	Biological activities and mechanisms of actions
cyclopamine	0,965	0,001	Hedgehog signaling inhibitor	0,509	0,036	Respiratory analeptic
		0,003	CYP17 inhibitor	0,477	0,013	CYP7 inhibitor
	0,725	0,005	Ovulation inhibitor	0,473	0,009	UGT2B7 substrate
	0,735	0,020	Antineoplastic	0,460	0,001	Smo receptor antagonist
	0,720	0,013	Oxidoreductase inhibitor	0,521	0,070	Nicotinic alpha4beta4 receptor agonist
	0,701	0,001	Antineoplastic (bone cancer)	0,499	0,052	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
	0,663	0,030	CYP3A substrate	0,450	0,009	Antineoplastic (ovarian cancer)
	0,671	0,065	Testosterone 17beta-dehydrogenase (NADP+) inhibitor	0,481	0,048	Antinociceptive
	0,639	0,034	CYP3A4 substrate	0,536	0,113	CYP2J substrate
	0,622	0,023	CYP3A5 substrate	0,459	0,046	Alcohol O-acetyltransferase inhibitor
	0,575	0,015	Prostate disorders treatment	0,417	0,004	Antineoplastic (gastric cancer)
	0,565	0,008	Menopausal disorders treatment	0,435	0,024	CYP3A7 substrate
	0,560	0,009	DELTA14-sterol reductase inhibitor	0,401	0,011	Prostatic (benign) hyperplasia treatment
	0,556	0,013	CYP2A11 substrate	0,422	0,040	Antimetastatic
	0,592	0,052	Phosphatase inhibitor	0,407	0,031	UGT1A substrate
	0,550	0,012	Gestagen antagonist	0,413	0,037	P-glycoprotein substrate
	0,567	0,033	Immunosuppressant	0,406	0,048	Bilirubin oxidase inhibitor
	0,567	0,036	Acetylcholine neuromuscular blocking agent	0,458	0,100	CYP3A2 substrate
	0,551	0,023	CYP3A inducer	0,406	0,050	Transcription factor NF kappa B stimulant
	0,531	0,010	Myc inhibitor	0,406	0,050	Transcription factor stimulant
	0,532	0,013	Interleukin 2 agonist	0,444	0,099	CYP2C12 substrate
	0,535	0,025	Dermatologic	0,389	0,046	Calcium regulator
	0,515	0,011	UGT1A4 substrate	0,429	0,086	Lysase inhibitor
	0,527	0,026	CYP3A4 inducer	0,455	0,127	CYP2J2 substrate

Continuation of table 5

	0,497	0,006	Antineoplastic (non-small cell lung cancer)	0,472	0,153	Antieczematic
	0,499	0,014	Antineoplastic (lung cancer)	0,418	0,100	Glyceryl-ether monooxygenase inhibitor
	0,481	0,005	Steroid synthesis inhibitor	0,458	0,155	CYP2H substrate
veratramine	0,725	0,004	CYP17 inhibitor	0,501	0,014	Myc inhibitor
	0,714	0,014	Oxidoreductase inhibitor	0,503	0,031	Dermatologic
	0,681	0,007	Ovulation inhibitor	0,484	0,018	CYP2A11 substrate
	0,670	0,007	UGT1A4 substrate	0,487	0,044	Antinociceptive
	0,667	0,021	Immunosuppressant	0,487	0,057	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
	0,650	0,017	UDP-glucuronosyltransferase substrate	0,472	0,042	Alcohol O-acetyltransferase inhibitor
	0,629	0,012	Antihypercholesterolemic	0,461	0,033	CYP3A inducer
	0,658	0,070	Testosterone 17beta-dehydrogenase (NADP+) inhibitor	0,443	0,026	UGT1A substrate
	0,569	0,033	General pump inhibitor	0,531	0,114	CYP2J substrate
	0,542	0,011	Interleukin 2 agonist	0,422	0,013	UGT2B7 substrate
	0,541	0,010	Menopausal disorders treatment	0,425	0,022	UGT2B4 substrate
	0,598	0,087	Antieczematic	0,431	0,030	P-glycoprotein substrate
	0,517	0,009	CYP7 inhibitor	0,434	0,039	CYP3A4 inducer
	0,521	0,015	Gestagen antagonist	0,495	0,112	Phosphatase inhibitor
	0,523	0,019	Prostate disorders treatment	0,450	0,130	CYP2J2 substrate
	0,511	0,013	DELTA14-sterol reductase inhibitor	0,420	0,125	Acetylcholine neuromuscular blocking agent
	0,526	0,033	CYP3A5 substrate	0,409	0,134	CYP3A2 substrate
jervine	0,939	0,001	Hedgehog signaling inhibitor	0,503	0,022	Transcription factor stimulant
	0,759	0,009	Oxidoreductase inhibitor	0,532	0,055	Acetylcholine neuromuscular blocking agent
	0,718	0,004	CYP17 inhibitor	0,491	0,040	Respiratory analeptic
	0,702	0,026	Antineoplastic	0,461	0,010	UGT2B7 substrate
	0,655	0,009	Ovulation inhibitor	0,474	0,028	Bilirubin oxidase inhibitor
	0,652	0,015	CYP3A inducer	0,482	0,043	Cholesterol antagonist
	0,630	0,001	Antineoplastic (bone cancer)	0,454	0,016	CYP7 inhibitor

Continuation of table 5

	0,656	0,031	CYP3A substrate	0,488	0,057	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
	0,634	0,016	CYP3A4 inducer	0,444	0,014	UGT1A4 substrate
	0,624	0,036	CYP3A4 substrate	0,447	0,018	Antineoplastic (lung cancer)
	0,641	0,075	Testosterone 17beta-dehydrogenase (NADP+) inhibitor	0,435	0,008	Steroid synthesis inhibitor
	0,603	0,046	Phosphatase inhibitor	0,462	0,040	Dermatologic
	0,551	0,009	Menopausal disorders treatment	0,499	0,081	Nicotinic alpha4beta4 receptor agonist
	0,535	0,015	CYP2A11 substrate	0,485	0,068	General pump inhibitor
	0,541	0,031	CYP3A5 substrate	0,426	0,010	Antineoplastic (ovarian cancer)
	0,517	0,012	Myc inhibitor	0,444	0,052	Alcohol O-acetyltransferase inhibitor
	0,517	0,015	Gestagen antagonist	0,429	0,038	Antimetastatic
	0,518	0,019	Prostate disorders treatment	0,451	0,070	Antinociceptive
	0,514	0,016	Interleukin 2 agonist	0,403	0,031	UGT1A substrate
	0,532	0,037	Immunosuppressant	0,400	0,035	CYP3A7 substrate
	0,498	0,015	DELTA14-sterol reductase inhibitor	0,491	0,130	CYP2H substrate
	0,503	0,022	Transcription factor NF kappa B stimulant			
3-angeloylzygadenine	0,658	0,024	Phosphatase inhibitor	0,619	0,078	Antieczematic
	0,664	0,046	CYP2H substrate	0,523	0,018	Antihypertensive
	0,613	0,004	Myc inhibitor	0,441	0,027	P-glycoprotein substrate
	0,581	0,011	Cardiotonic	0,409	0,022	Antineoplastic (lung cancer)
	0,562	0,018	Polarisation stimulant	0,464	0,083	Antineoplastic
3-veratroylzygadenine	0,841	0,011	CYP2H substrate	0,547	0,008	Myc inhibitor
	0,687	0,050	Antieczematic	0,460	0,046	Polarisation stimulant
	0,627	0,035	Phosphatase inhibitor	0,439	0,028	P-glycoprotein substrate
	0,581	0,011	Cardiotonic	0,428	0,267	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,562	0,013	Antihypertensive	0,516	0,038	Apoptosis agonist
15-angeloylgermine	0,633	0,004	Myc inhibitor	0,468	0,016	Antineoplastic (lung cancer)
	0,645	0,028	Phosphatase inhibitor	0,461	0,027	Antihypertensive
	0,654	0,048	CYP2H substrate	0,454	0,023	P-glycoprotein substrate

Continuation of table 5

	0,593	0,047	Antineoplastic	0,416	0,033	Cardiotonic
	0,553	0,020	Polarisation stimulant	0,404	0,109	Glyceryl-ether monooxygenase inhibitor
	0,581	0,095	Antieczematic	0,468	0,020	P-glycoprotein substrate
Germine	0,709	0,034	CYP2H substrate	0,463	0,024	Cardiotonic
	0,657	0,024	Phosphatase inhibitor	0,427	0,020	Antineoplastic (lung cancer)
	0,618	0,004	Myc inhibitor	0,435	0,045	Dermatologic
	0,533	0,024	Polarisation stimulant	0,410	0,035	H+-transporting two-sector ATPase inhibitor
	0,517	0,019	Antihypertensive	0,453	0,081	Glyceryl-ether monooxygenase inhibitor
	0,580	0,095	Antieczematic	0,406	0,045	Antimetastatic
Veratrosine	0,854	0,018	CDP-glycerol glycerophosphotransferase inhibitor	0,457	0,015	Levansucrase inhibitor
	0,780	0,005	Antihypercholesterolemic	0,459	0,022	P-glycoprotein substrate
	0,771	0,009	UDP-glucuronosyltransferase substrate	0,471	0,036	Analeptic
	0,754	0,010	Immunosuppressant	0,461	0,028	Dolichyl-diphosphooligosaccharide-protein glycotransferase inhibitor
	0,714	0,014	Oxidoreductase inhibitor	0,442	0,013	Mannosyl-glycoprotein endo-beta-N-acetylglucosaminidase inhibitor
	0,706	0,035	CYP2H substrate	0,474	0,049	Antineoplastic (non-Hodgkin's lymphoma)
	0,692	0,031	Benzoate-CoA ligase inhibitor	0,496	0,073	Antineoplastic
	0,644	0,014	Cholesterol antagonist	0,416	0,007	Vascular dementia treatment
	0,638	0,010	Lactase inhibitor	0,441	0,041	Antifungal
	0,626	0,007	CYP17 inhibitor	0,436	0,036	Antimetastatic
	0,596	0,005	Interleukin 2 agonist	0,441	0,044	Dermatologic
	0,612	0,022	Respiratory analeptic	0,432	0,037	Caspase 8 stimulant
	0,608	0,026	Glyceryl-ether monooxygenase inhibitor	0,404	0,013	Phospholipase A1 inhibitor
	0,588	0,019	CYP3A inducer	0,421	0,034	Prostate disorders treatment
	0,580	0,020	CYP3A4 inducer	0,428	0,043	Membrane permeability enhancer
	0,561	0,007	Myc inhibitor	0,411	0,027	Chloride channel blocker
	0,569	0,015	Antiviral (Influenza)	0,412	0,030	Gestagen antagonist

Continuation of table 5

	0,564	0,013	Proliferative diseases treatment	0,494	0,114	Phosphatase inhibitor
	0,588	0,042	Anaphylatoxin receptor antagonist	0,400	0,022	Chemopreventive
	0,555	0,014	Antinociceptive	0,460	0,084	General pump inhibitor
		0,014	Transcription factor NF kappa B stimulant	0,409	0,033	Lipid peroxidase inhibitor
	0,551	0,014	Transcription factor stimulant	0,404	0,029	Antibacterial
	0,563	0,029	CYP3A5 substrate	0,403	0,031	Hepatoprotectant
	0,543	0,015	Mycothiol-S-conjugate amidase inhibitor	0,418	0,046	Antithrombotic
	0,532	0,024	Aspartyltransferase inhibitor	0,384	0,018	Protein synthesis inhibitor
	0,512	0,012	Dementia treatment	0,442	0,076	Antiinflammatory
	0,509	0,013	CYP2C9 inducer	0,435	0,076	Alkenylglycerophosphocholine hydrolase inhibitor
	0,499	0,019	Anticarcinogenic	0,464	0,157	Antieczematic
	0,511	0,035	Beta glucuronidase inhibitor	0,404	0,137	CYP3A2 substrate
	0,497	0,023	Bilirubin oxidase inhibitor	0,558	0,013	Bilirubin oxidase inhibitor
Pseudojevine	0,897	0,001	Hedgehog signaling inhibitor	0,552	0,014	Mycothiol-S-conjugate amidase inhibitor
	0,849	0,020	CDP-glycerol glycerophosphotransferase inhibitor	0,548	0,017	Antiviral (Influenza)
	0,802	0,004	Cholesterol antagonist	0,581	0,057	Phosphatase inhibitor
	0,795	0,009	Respiratory analeptic	0,527	0,023	Antinociceptive
	0,764	0,017	Antineoplastic	0,527	0,025	Aspartyltransferase inhibitor
	0,757	0,009	Oxidoreductase inhibitor	0,514	0,012	Dementia treatment
	0,745	0,010	CYP3A4 inducer	0,497	0,002	Antineoplastic (bone cancer)
	0,739	0,010	CYP3A inducer	0,554	0,066	TP53 expression enhancer
	0,724	0,031	CYP2H substrate	0,504	0,037	Beta glucuronidase inhibitor
	0,692	0,018	Immunosuppressant	0,481	0,021	Proliferative diseases treatment
Tomatillidine	0,652	0,011	Antiprotozoal (Leishmania)	0,480	0,022	Caspase 8 stimulant
	0,650	0,014	Analeptic	0,482	0,024	Antimetastatic
	0,628	0,007	CYP17 inhibitor	0,472	0,015	Antineoplastic (lung cancer)
	0,627	0,009	Chemopreventive	0,476	0,025	Dolichyl-diphosphooligosaccharide-protein glycotransferase inhibitor

Continuation of table 5

	0,644	0,037	Benzoate-CoA ligase inhibitor	0,511	0,060	CYP3A4 substrate
	0,613	0,008	Transcription factor NF kappa B stimulant	0,447	0,016	Levansucrase inhibitor
	0,613	0,008	Transcription factor stimulant	0,430	0,014	Mannosyl-glycoprotein endo-beta-N-acetylglucosaminidase inhibitor
	0,616	0,011	Lactase inhibitor	0,417	0,007	Vascular dementia treatment
	0,635	0,034	CYP3A substrate	0,437	0,028	P-glycoprotein substrate
	0,609	0,012	Hepatoprotectant	0,432	0,023	CYP2A11 substrate
	0,614	0,037	Anaphylatoxin receptor antagonist	0,426	0,033	Prostate disorders treatment
	0,580	0,007	Interleukin 2 agonist	0,404	0,014	Phospholipase A1 inhibitor
	0,596	0,029	Glyceryl-ether monooxygenase inhibitor	0,415	0,029	Gestagen antagonist
	0,570	0,006	Myc inhibitor	0,447	0,074	Antiinflammatory
	0,580	0,027	CYP3A5 substrate	0,410	0,069	Apoptosis agonist
	0,575	0,022	UDP-glucuronosyltransferase substrate	0,406	0,136	CYP3A2 substrate

CONCLUSION

Plants and their phytopharmaceuticals used by mankind from centuries in the treatment of ailments. Plant synthesize thousands of secondary metabolites in natural pathways therefore induce less toxicity and side effects as compared to synthetic drugs. Intense research on ethnobotanicals will not only achieve definitive knowledge about the plant and its biological properties but also it may facilitate the synthesis of more potent novel drugs with high efficacy and reduced toxicity. The conventional procedure for drug discovery is long design cycle, time consuming and cost effective therefore the early inclusion of pharmacokinetics consideration in the drug discovery process by in silico methods using improved generation of software's is becoming popular as the benefits they provide in high throughput and early application in drug design are realized. . Subsequently there is always a need to screen a number of plants with medicinal value for promising biological activity. In present study we have analyzed ten isolated alkaloids from *Veratrum* dahuricum through Pharmacoinformatics and Chemoinformatic approach. It is interesting to reveal That the pharmacophore properties of the ten compounds where found to be obeying the Lipinski rule of five parameters significantly and The ADMET prediction using admetSAR revealed that all the compounds were in the acceptable range having no or less toxic effects with many mechanisms of action and biological activities. Such screening of plants can provide novel sources of new bioactive compounds with functional properties beneficial to restore health. However further In vitro and In vivo analysis of each compound for various pharmacological benefits can be carried out for the discovery of novel drug compounds.

REFERENCES

Al Haddad and Asma Ahmad (2015), "Virtual Screening of Phytochemicals for Cancer Therapy, 2015. *Teses.* Paper 241

Balakin KV, Ivanenkov YA, Savchuk NP, Ivashchenko AA, Ekins S(2005). Comprehensive computational assessment of ADME properties using mapping techniques. Current Drug Discovery Technologies. 2005 Jun 1;2(2):99-113.

Balasundaram A, Ragupathy R, Sankar S, Thiyagarajan M, Ravi L, Karuppasamy R, and Veerappapillai S., (2016) Investigation of Phytocompounds and Computational Approach for the Evaluation of Therapeutic Properties of Ethanolic Leaf Extract of *Callistemon citrinus.,* Int. J. Pharm. Sci. Rev. Res., 37(1), April 2016; Article No. 20,

Baldi A. Computational approaches for drug design and discovery: an overview. Systematic Reviews in Pharmacy. 2010 Jan 1;1(1):99.

Chaudhary G ,Goyal S, Poonia P and Lawsoniainermis Linnaeus (2010): a phytopharmacological review. Int J Pharm Sci Drug Res.

2010;2(2):91-8.
Chen H, Yao K, Nadas J, Bode AM, Malakhova M, Oi N, Li H and Lubet RA and Dong (2012).. Prediction of molecular targets of cancer preventing flavonoid compounds using computational methods. PloS one. 2012 May 31;7(5):e38261.
Cong Y, Li J, Zhang QC, Guo JG and Li SS (2015). Steroidal Alkaloids from *Veratrum* dahuricum (Turcz.) Loes. f. with Genotoxicity on Brain Cell DNA in Mice. Helvetica ChimicaActa. 2015 Jan 1;98(1):85-91.
De Fátima A, Modolo LV, Conegero LS, Pilli RA,Ferreira CV, Kohn LK *et al*. Styryl lactones and their derivatives: biological activities, mechanisms of actionand potential leads for drug design. Current medicinalchemistry. 2006; 13(28):3371-84.
Garaniya N and Bapodra A.(2014) Ethno botanical and Phytophrmacological potential of Abrusprecatorius L.: A review. Asian Pacific journal of tropical biomedicine. 2014 May 31;4:S27-34.
Goel RK, Singh D, Lagunin A and Poroikov V.(2011) PASS-assisted exploration of new therapeutic potential of natural products. Medicinal Chemistry Research. 2011 Dec 1;20(9):1509-14.
Gu R, Wang Y, Long B, Kennelly E, Wu S, Liu B, Li P and Long C.(2014). Prospecting for bioactive constituents from traditional medicinal plants through ethnobotanical approaches. Biological and Pharmaceutical Bulletin. 2014;37(6):903-15.
Higgins J, Cartwright ME and Templeton AC(2012). Progressing preclinical drug candidates: strategies on preclinical safety studies and the quest for adequate exposure. Drug discovery today. 2012 Aug 31;17(15):828-36.
Jamkhande PG, Wattamwar AS, Pekamwar SS, Chandak PG. Antioxidant, antimicrobial activity and in silico PASS prediction of Annona reticulata Linn. root extract. Beni-Suef University Journal of Basic and Applied Sciences. 2014 Jun 30;3(2):140-8.
Jayachitra A, Muniyandi MJ. Journal of Pharmacological and Toxicological Investigations. Journal of Pharmacological and Toxicological Investigations. 2015 Dec;1(3).
Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies. 2004 Dec 31;1(4):337-41.
Lombardo F, Gifford E, Shalaeva MY. In silico ADME prediction: data, models, facts and myths. Mini reviews in medicinal chemistry. 2003 Dec 1;3(8):861-75.
Ntie-Kang F. An in silico evaluation of the ADMET profile of the StreptomeDB database. SpringerPlus. 2013 Jul 30;2(1):1.
Paramashivam SK, Elayaperumal K, Natarajan BB, Ramamoorthy MD, Balasubramanian S and Dhiraviam KN(2015). In silico pharmacokinetic and molecular docking studies of small molecules derived from IndigoferaaspalathoidesVahl targeting receptor tyrosine kinases. Bioinformation. 2015 Feb 28;11(2):73-84.
Polachi, N., Nagaraja, P., Subramaniyan, B. And Mathan, G.,(2015). Antiproliferative activity of N-butanol floral extract from butea monosperma against hct 116 colon cancer cells; drug likeness properties and in silico evaluation of their active compounds toward glycogen synthase kinase-3β/axin and β-catenin/T-cell factor-4 protein complex. *Asian J Pharm Clin Res*, *8*(1): 134-141.
Riju A, Sithara K, Nair SS, Shamina A, and EapenSJ(2009). In silico screening major spice phytochemicals for their novel biological activity and pharmacological fitness. Journal of Bioequivalence & Bioavailability. 2011 Jun 20;2009.
Sofi MS, Sateesh MK, and Bashir M(2014). Screening of the Ethnobotanicals against MDA-MB-231 and MCF-7 breast cancer cell lines. International Journal of Phytopharmacy. 2014 Dec 30;4(6):140-7.
Suhail Mohammed Hussain, Arbaaz Ahmed l., Shrihith A. and Sateesh M. K.(2016) computational approach for the evaluation of bioactive compounds from ethnobotanicals for their pharmacological potential and biological activity.world journal of pharmacy and pharmaceutical sciences. 2016, 5(12): 1042-1056.
Suhail Mohammed Hussain, Mohammed Sadath Hussain, Arbaaz Ahmed L and NahidaArif(2016). Characterization of isolated bioactive phytoconstituentsfrom *Flacourtiaindica* as potential phytopharmaceuticals - An *in silico* perspective. Journal of Pharmacognosy and Phytochemistry 2016; 5(6): 323-331
Tang J, Li HL, Shen YH, Jin HZ, Yan SK, Liu XH, Zeng HW, Liu RH, Tan YX and Zhang WD(2010). Antitumor and antiplatelet activity of alkaloids from *Veratrum* dahuricum. Phytotherapy Research. 2010 Jun 1;24(6):821-6.
Tang J, Li HL, Shen YH, Jin HZ, Yan SK, Liu XH, Zeng HW, Liu RH, Tan YX and Zhang WD(2010). Antitumor and antiplatelet activity of alkaloids from *Veratrum* dahuricum. Phytotherapy Research. 2010 Jun 1;24(6):821-6.
Trisilowati, and Mallet D. G(2012). In silico experimental modeling of cancer treatment. ISRN oncology. 2012 Feb 1;2012.
Ververidis F, Trantas E, Douglas C, Vollmer G, Kretzschmar G and PanopoulosN(2007). Biotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I: Chemical diversity, impacts on plant biology and human health. Biotechnology journal. 2007 Oct 1;2(10):1214-34.
World Health Organization. WHO traditional medicinestrategy 2002-2005.
Xuetao MA, Liu M, Wu Z, and Li Y(2015). Anti-proliferative activity of active constituents in *Veratrum* dahuricum on human bladder cancer T24 cells. Biomedical Research. 2015;26(4):672-6.