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IN-SILICO STUDIES ON CHEMICAL CONSTITUENTS OF *CALOTROPIS* SPECIES

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Keywords:

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ABSTRACT: Nowadays, the use of herbal drugs is tremendously increased due to the lesser number of side effects when compared to pure form of drugs. Herbal medicine is a complex compound with multiple synergistic mechanisms of action which modulate pathophysiological functions. Even though few herbs exhibit toxicity, they possess many therapeutic values and curative principles; one such herb is calotropis. It exists in three species that produce pharmacological effects: cardiovascular, anti-cancer, antimicrobial, anticonvulsant, and smooth muscle relaxant. In this research, 24 chemical constituents of all calotropis species were selected. The molecular properties, bioactivity scores, ADMET profile of 24 calotropis species chemical constituents were predicted using computational tools, including mol inspiration, Pre ADMET, and structures drawn using chem sketch. The results drawn from the study were compounds C_8[Syriogenin] and C_{16}[urosolic acid] exhibited good oral bioavailability, bioactivity scores, intestinal absorption, renal absorption, decreased metabolism rate by inhibiting CYP3A4 and less toxic by Ames test.

INTRODUCTION: Herbal medicine is an interdisciplinary branch that deals with herbs with medicinal values related to various branches, including botany, medicinal plant research, phytochemistry, pharmacognosy, ayurveda, natural chemistry, agriculture science, Unani medicines, biotechnology and biochemistry [1]. Herbal medicine is defined as the use of plants to prevent and treat illness or achieve good health and the drugs and tinctures used. The major use of herbal medicines is for health promotion and therapy for chronic as opposed to life-threatening conditions. Traditional medicines are widely perceived as natural and safe, that is not toxic [2].

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Currently, herbs are applied to treat chronic and acute conditions and various ailments and problems such as cardiovascular disease, prostate problems, depression, and inflammation and to boost the immune system, to name but a few [3]. Various herbs have different pharmacological actions, including antiulcer, anticonvulsant, irregular heartbeat, anti-inflammatory insomnia, anxiety, CNS depressant effect migraine, *etc*. Among all the most widely used herbs, herbs belonging to the family *Asteracae, Solanaceae, Umbelliferace,* and *Laminacae* exhibit diverse pharmacological properties [4-5].

An *in-silico* study is one performed *via* stimulation on a computer. The various methods include data-based quantitative structure, activity relationship, pharmacophores, homology, models and other molecular modeling approaches, machine leading, data mining, and network analysis tools we use a computer. Such models have seen frequent use in

discovering and optimizing novel molecules with affinity to a target, classifying absorption, distribution, metabolism, excretion, and toxicity properties, as well as physicochemical characterization [6, 7]. It provides a platform for screening the activity of potential therapeutics against the molecular targets, which helps to select the one with the highest potential activity for further *in-vitro* and *in-vivo* experiments focusing on only selected targets will reduce the cost for laboratory trail, that requires financial and human resources. *In-silico* studies are recently widely used to study the complexities in oxidative stress-induced pathology [8-10]. Based on the need for herbal medicines to treat various pathological conditions and the importance of computational tools in drug discovery, the work was carried out on one of such herbs belonging to the family *Apocynaceae*. The selected herb was *Calotropis*; it exhibits various pharmacological properties despite its toxicity due to its latex [11-14]. The study aimed to perform *in-silico* screening by predicting the physicochemical and pharmacokinetic properties of chemical constituents of *Calotropis* species.

METHODOLOGY:

Chemical Structures and Generation of Smiles Notation: Among all the *Calotropis* species, only 24 compounds are selected based on the availability of structures in Pubchem and journals. Structures of chemical constituents of *Calotropis* species about 24 (C_1-C_{24}) were drawn by using chem sketch and Chem Draw ultra 12.0 computational tools. SMILES compound (C_1-C_{24}) notations were generated using chem sketch [15, 16].

Prediction of Molecular Properties and Bioactivity Scores: All the selected 24 chemical constituents of *Calotropis* species were predicted for their molecular properties and bioactivity scores by using an online web server (www. molinspiration.com) mol inspiration *in-silico* tool [17]. By using SMILES notation of all the selected chemical constituents (C_1-C_{24}), molecular properties and bioactivity scores were predicted.

Molecular properties including molecular weight, topological polar surface area (TPSA), number of Nitrogen atoms, number of oxygen atoms, number of OH atoms, number of NH atoms, partition coefficient (miLogP), number of rotatable bonds, volume, number of violations. According to Lipinski rule of five. Molecular weight less than 500 Daltons, milogP less than or equal to 5, no. of Hydrogen bond donors less than or equal to 5, no. of hydrogen bond acceptor less than or equal to 10 indicates the chemical compound possesses good oral bioavailability.

Bioactivity scores SMILES notation of 24 compounds was used to predict bioactivity were predicted based on the activity scores of G-protein coupled receptor, ion channel modulator, kinase I, nuclear receptor ligand, protease I, and enzyme I. Bioactivity scores range from 0 to -0.5 indicating moderately active; bioactivity scores less than -0.5 indicates less activity; bioactivity score greater than 0, indicates highly active [17, 18].

Prediction of ADMET Properties: ADMET includes absorption, distribution, metabolism, elimination properties and toxicity profile of all the 24 chemical constituents (C_1-C_{24}) of *Calotropis* species were predicted by using online web server (www.PreADMET.com) PreADMET [19-22] and admet SAR [21-23].

Prediction of Absorption, Distribution and Elimination Properties: Pre-ADMET uses various models of *in-vivo* and *in-vitro* prediction techniques to predict oral absorption. Basic models include PSA, rapid PSA, and other complex models. Predicting tissue distribution can promote the investigation of pharmacodynamics and toxicokinetics.

Distribution prediction is mainly related to the blood-brain barrier (BBB) permeability, apparent volume of distribution (VD), and plasma protein binding (PPB). Many of these models are developed based on the three-dimensional crystal structure of albumin, which can be used for docking studies to predict the binding of molecules to albumin. Quantitative structure-activity relationship (QSAR) models are developed based on the existing data of various ligands known to bind albumin.

These computational models can accurately predict the interaction of molecules with human serum albumin.

Prediction of Metabolism and Toxicity Profile: The metabolic process is a very complex process involving various enzyme activities and differs due to different genetic factors; we use different calculation models to predict the metabolism of some drugs. CYP enzyme affinity towards the ligands can be predicted. After carrying out the drug excretion/elimination prediction, the collected information must be integrated into the predictive model to provide a complete model to describe the substance behaviour at different stages of drug discovery and development.

Toxicity prediction with professional knowledge in computational toxicity. Groups perform QSAR modeling through the use of toxicity databases. Drug toxicity prediction can effectively reduce the need for animal testing. Pre-ADMET can predict both systemic toxicity and the toxicity of certain organs in addition to carcinogenicity and genotoxicity.

RESULTS AND DISCUSSION:

Chemical Structures and Generation of Smiles Notation: All 24 selected chemical compounds C_1-C_{24} structures were drawn, and smiles notations were generated using the computational tool chem sketch. The data was presented in **Table 1** and structures are displayed in **Fig. 1.**

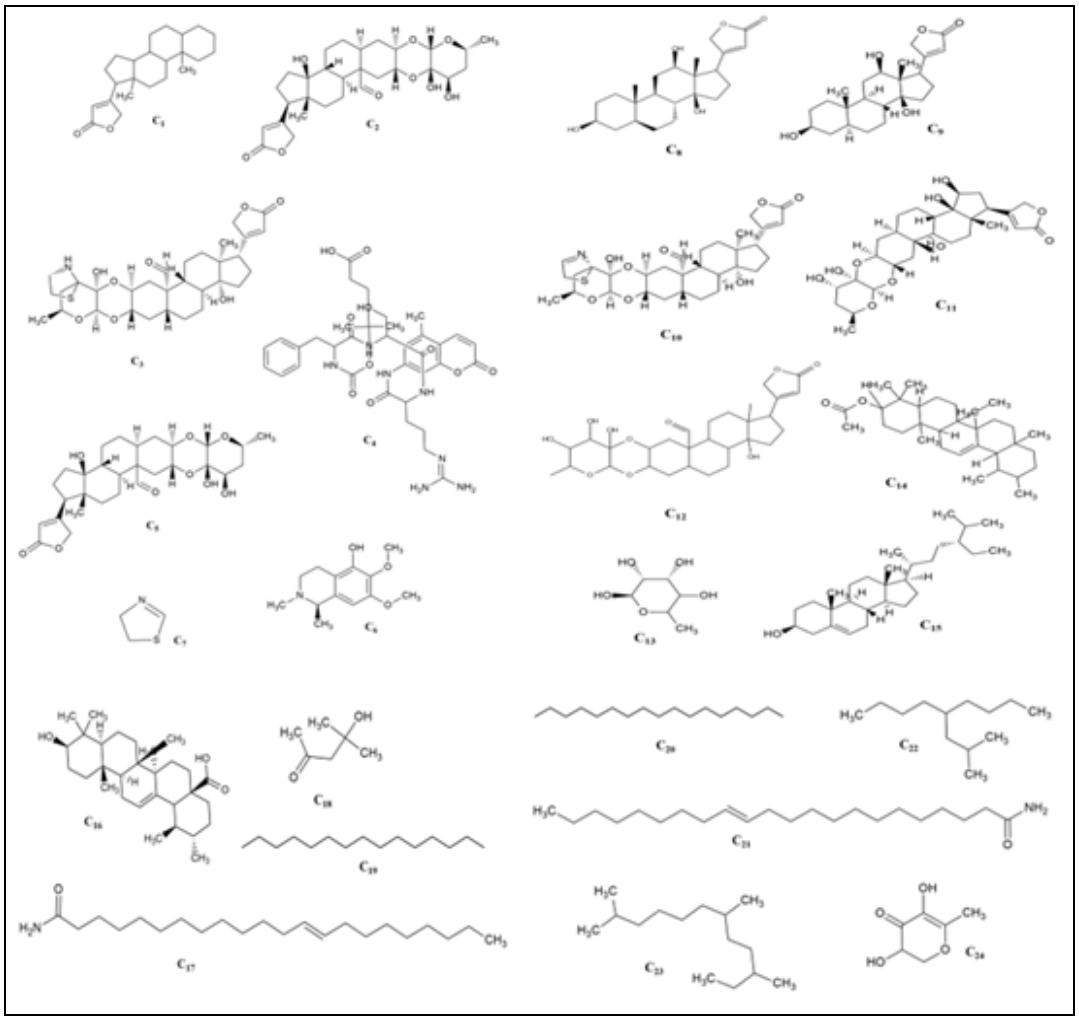

FIG. 1: MOLECULAR STRUCTURES OF 24 COMPOUNDS

TABLE 1: CHEMICAL STRUCTURES OF COMPOUNDS C_1-C_{24}

Name of the Compound	Code	Name of the compound	Code
Cardenolide	C_1	L-rhamnose	C_{13}
Calotropin	C_2	Amyrin acetate	C_{14}
Voruscharin	C_3	Beta-sitositerol	C_{15}
Trypsin	C_4	Urosolic acid	C_{16}
Calactin	C_5	Octadecenamide	C_{17}

Gigantin	C_6	Tyranton	C_{18}
Thiazoline	C_7	Pentadecane	C_{19}
Syriogenin	C_8	Heptadecane	C_{20}
Uscharidin	C_9	Erucamide (z)-docos-13-enamide	C_{21}
Uscharin	C_{10}	Isobutyl nonane	C_{22}
Proceroside	C_{11}	2,7,10-Trimethyl dodecane	C_{23}
Calotoxin	C_{12}	2,3-dihydro-3,5-dihydroxy -6-methyl -4H-pyran-4-one	C_{24}

Molecular Properties and Bioactivity Scores: The molecular properties and bioactivity scores of compounds C_1-C_{24} were predicted busing molinspiration and results were represented in **Table 2** and **Table 3,** respectively. All the compounds obeyed Lipinski rule of five except **C_4**. The molecular weight of all compounds ranges from 115 to 665 Daltons, mi Log P values range from -0.46 to 8.79 and no violations indicate all the derivatives exhibited good oral bioavailability and drug-like properties. The bioactivity data revealed that all the chemical constituents were moderately active as enzyme and kinase inhibitors, inactive as ion channel modulators, and few chemical constituents displayed moderate scores towards protease inhibition, nuclear receptor inhibition, and GPCR ligand. Compounds $C_{13,}$ $C_{18,}$ C_{24} showed less bioactivity scores remaining compounds exhibited moderate to high scores ranging from -0.48 to 9.58.

TABLE 2: MOLECULAR PROPERTIES OF CHEMICAL CONSTITUENTS C_1-C_{24} OF *CALOTROPIS* SPECIES

Compound code	Mi Log P	TPSA	N atoms	MW	n OH	n OH NH	n Vio	N rtbs	Volume
C_1	4.80	26.30	25	342.5	2	0	0	1	348.90
C_2	1.15	131.76	38	532.63	9	3	1	2	480.72
C_3	2.01	123.56	41	589.75	9	3	1	2	525.67
C_4	2.78	240.47	48	665.75	15	9	3	16	605.62
C_5	1.15	131.76	38	532.63	2	3	1	2	480.72
C_6	1.82	41.93	17	237.30	4	1	0	2	228.65
C_7	0.55	12.36	5	87.15	1	0	0	0	76.79
C_8	1.56	86.99	28	390.52	5	3	0	1	372.68
C_9	0.96	128.60	38	530.61	9	2	1	2	474.86
C_{10}	2.09	123.90	41	587.74	9	2	1	2	519.73
C_{11}	0.23	151.99	39	548.63	10	4	1	2	488.77
C_{12}	0.42	151.99	39	548.63	10	4	1	2	488.77
C_{13}	1.64	90.15	11	164.16	5	4	0	0	143.55
C_{14}	8.58	26.30	34	468.77	2	0	1	2	497.56
C_{15}	8.62	20.23	30	414.72	1	1	1	6	456.52
C_{16}	6.79	57.53	33	456.71	3	2	1	1	471.49
C_{17}	7.30	43.09	20	281.48	2	2	1	15	322.11
C_{18}	0.31	37.30	8	116.16	2	1	0	2	122.62
C_{19}	8.19	0.00	15	212.42	0	0	1	12	264.18
C_{20}	8.79	0.00	17	240.47	0	0	1	14	297.78
C_{21}	8.74	43.09	24	337.59	2	2	1	19	389.32
C_{22}	6.40	0.00	13	184.37	0	0	1	8	230.15
C_{23}	6.16	0.00	15	212.42	0	0	1	9	263.54
C_{24}	-0.46	66.76	10	144.13	4	2	0	0	123.40

Mi Log P: lipophilicity, TPSA: topological polar surface area, n: number of, Mol. wt: molecular weight, vio: violations, rtbs: rotatable bonds.

TABLE 3: BIOACTIVITY SCORES OF COMPOUNDS C_1-C_{24} OF CALOTROPIS SPECIES

Compound code	GPCR ligand	Ion channel modulator	Kinase Inhibitor	Nuclear receptor ligand	Protease Inhibitor	Enzyme Inhibitor
C_1	0.11	0.12	0.48	0.39	0.17	0.63
C_2	0.07	0.01	0.29	0.52	0.12	0.88
C_3	0.10	0.40	0.62	0.07	0.03	0.61
C_4	0.18	1.05	0.83	0.90	0.36	0.45
C_5	0.07	0.01	0.29	0.52	0.12	0.88
C_6	0.02	0.09	0.51	0.65	0.46	0.08
C_7	3.73	3.90	3.91	3.98	3.71	3.71

C_8	0.16	0.14	0.36	0.51	0.02	0.80
C_9	0.05	0.16	0.45	0.37	0.63	0.74
C_{10}	0.08	0.33	0.54	0.15	0.03	0.67
C_{11}	0.08	0.02	0.28	0.46	0.14	0.76
C_{12}	0.04	0.11	0.34	0.35	0.07	0.80
C_{13}	-0.75	-0.15	-1.11	-1.11	-0.61	0.20
C_{14}	0.12	0.04	0.50	0.67	0.14	0.52
C_{15}	0.14	0.04	0.51	0.73	0.07	0.51
C_{16}	0.28	0.03	0.50	0.89	0.23	0.69
C_{17}	0.04	-0.04	-0.03	-0.04	0.02	0.19
C_{18}	-3.10	-2.69	-3.69	-2.73	-2.81	-2.35
C_{19}	-0.38	-0.07	-0.53	-0.45	-0.50	-0.13
C_{20}	-0.21	-0.01	-0.34	-0.25	-0.31	-0.04
C_{21}	0.11	-0.04	-0.03	0.06	0.18	0.10
C_{22}	-0.48	-0.17	-0.94	-0.60	-0.43	-0.20
C_{23}	-0.40	-0.08	-0.68	-0.41	-0.34	-0.14
C_{24}	-1.59	-0.96	-2.25	-1.60	-1.53	-0.65

GPCR: G-protein coupled receptors.

Absorption, Distribution and Elimination Properties: Absorption, distribution and elimination properties of all the 24 Compounds [C_1-C_{24}] were predicted by using PreADMET and data were listed in **Table 4**. Compound C_1-C_{24} showed %HIA ranging from 75-100, CaCO2 cell permeability from 22-57, and skin permeability from 1.72-4.49 cm/s. All the compounds are strongly bound to about 35-100 % plasma protein. Some chemical constituents showed P-glycoprotein I ranging from 38-100 %. Compounds C_3, C_6, C_7, C_{18}, C_{24} do not cross the blood-brain barrier [BBB] as their permeability is nearly 0.1; the compounds C_2, C_{20}, C_{23}, C_{25} penetrate BBB.

TABLE 4: ABSORPTION, DISTRIBUTION AND ELIMINATION PROPERTIES OF COMPOUNDS C_1-C_{24}

Compound Code	$CaCO_2$ Permeability	MDCK	HIA	Skin Permeability	BBB	% PPB	P-gp
C_1	32.13	72.66	100.00	-1.48	13.52	100.0	I
C_2	57.70	56.53	100.00	-2.15	21.24	100.0	I
C_3	15.59	0.043	94.60	-4.49	0.064	95.80	I
C_4	49.25	0.043	97.83	-3.20	3.93	92.38	I
C_5	57.81	58.26	100.00	-2.32	23.18	100.0	I
C_6	51.57	357.69	94.74	-3.18	0.715	47.21	NI
C_7	53.05	3.470	97.45	-3.71	0.72	52.92	NI
C_8	22.20	66.19	100.00	-1.02	16.63	100.0	I
C_9	22.2	66.02	100.00	-1.12	16.53	100.0	I
C_{10}	49.25	0.043	97.83	-3.20	3.93	92.37	I
C_{11}	38.19	115.8	100.00	-2.34	3.43	93.32	I
C_{12}	48.56	0.04	98.49	-2.21	8.75	96.45	I
C_{13}	27.87	153.2	100.00	-1.72	2.19	100.0	NI
C_{14}	23.64	112.4	100.00	-1.08	9.58	100.0	I
C_{15}	23.40	67.45	100.00	-1.42	18.19	100.0	I
C_{16}	22.2	66.51	100.00	-1.14	16.95	100.0	I
C_{17}	29.31	72.90	95.32	-0.56	10.40	100.0	I
C_{18}	1.06	122.3	85.33	-0.40	0.32	66.82	NI
C_{19}	22.19	67.97	100.00	-0.52	25.13	100.0	I
C_{20}	22.19	66.02	100.00	-0.49	25.52	100.0	I
C_{21}	40.79	68.44	95.34	-0.52	19.25	100.0	I
C_{22}	22.19	66.77	100.00	-0.58	16.42	100.0	I
C_{23}	22.19	67.91	100.00	-0.54	20.44	100.0	I
C_{24}	1.85	24.09	75.91	-4.75	0.27	38.43	I

MDCK- madin-darby canine kidney, HIA- Human intestinal absorption, P-gp- Plasma glycoprotein, I- Inhibitor, NI- Non-Inhibitor

Metabolism and Toxicity Profile: CYP450 enzymes metabolize most medications; the most important of these enzymes are CYP2C9, CYP2C19, and CYP3A4. Metabolism and toxicity of compound C_1-C_{24} were reported in **Table 5**. All the compounds except C_6 acts as I for the enzyme

CYP2C9, CYP2C19, CYP2D6 and CYP3A4, respectively and C_1, C_{17}, C_{21} compounds displayed the all types of CYP2C,2D and 3A4 enzyme inhibition.

Mutagenicity was predicted to all the compounds by using the AMES test. Among all these 24 compounds C_1, C3, C_8, C_9, C_{11}, C_{16}, C_{19}, C_{20}, C_{21}, C_{17} do not exhibited mutagenicity. All the constituents have low to medium risk associated with HERG inhibition.

TABLE 5: METABOLISM AND TOXICITY PROPERTIES OF COMPOUNDS C_1-C_{24}

Compound Code	CYP2C19	CYP2C9	CYP2D6	CYP3A4	AMES mutagen	HERG inhibition
C_1	I	I	I	I	No	LR
C_2	NI	I	NI	I	Yes	MR
C_3	NI	I	NI	I	No	LR
C_4	NI	I	NI	I	Yes	LR
C_5	NI	I	I	I	Yes	MR
C_6	NI	NI	NI	NI	Yes	LR
C_7	I	I	NI	I	Yes	LR
C_8	NI	I	NI	I	No	MR
C_9	NI	I	NI	I	No	MR
C_{10}	NI	I	NI	I	Yes	LR
C_{11}	NI	I	NI	I	No	LR
C_{12}	NI	I	NI	I	Yes	LR
C_{13}	NI	I	NI	I	Yes	MR
C_{14}	NI	I	NI	I	Yes	LR
C_{15}	NI	I	NI	NI	No	LR
C_{16}	NI	I	NI	I	No	MR
C_{17}	I	I	I	I	No	LR
C_{18}	I	I	NI	I	Yes	LR
C_{19}	I	I	NI	I	No	MR
C_{20}	I	I	NI	I	No	MR
C_{21}	I	I	I	I	No	LR
C_{22}	I	I	NI	I	Yes	MR
C_{23}	I	I	NI	I	Yes	MR
C_{24}	NI	I	NI	NI	Yes	LR

CYP- cytochrome P 450 class of enzymes, LR-Low risk, MR- Medium risk.

CONCLUSION: The various computational tools used to predict molecular properties, Bioactivity scores, ADMET properties of the 24 chemical constituents [C_1-C_{24}] of *calotropis* species were selected based on their structure availability from pub chem databases and from articles published in journals. All the structures were drawn by using a chem sketch. Chemical constituents C_1-C_{24} obeyed Lipinski's rule of five and exhibited good oral bioavailability. All compounds displayed moderate to high bioactivity scores towards the GPCR ligand, ion channel modulator, kinase, and protease enzymes. Among all, only 19 compounds showed BBB penetration. Except C_3, C_4, C_{10}, C_{12} remaining compounds are sensitive to MDCK, indicating good renal absorption. Mostly all the compounds C_1, C_2, C_5, C_8, C_9, C_{11}, C_{13}, C_{14}, C_{15}, C_{16}, C_{19}, C_{20}, C_{22}, C_{23} possess 100% human intestinal absorption. All the compounds having $CaCO_2$ permeability and C_1, C_2, C_5, C_8, C_9, C_{13}, C_{14}, C_{15}, C_{16}, C_{19}, C_{20},C_{21}, C_{22}, C_{23} having 100% plasma protein binding. All the compounds except C_6, C_7, C_{13}, C_{18} are P-gp inhibitors, indicating that the duration of action increases. Few compounds exhibited mutagenicity with AMES test and low to high risk produced with HERG inhibition.

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CONFLICTS OF INTEREST: Nil

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