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Research Article

In silico ADME and Drug-likeness Evaluation of Phytochemicals from the Leaves of *Tabernaemontana divaricata* Linn.

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ABSTRACT

Introduction: *Tabernaemontana divaricata* is a traditional plant from the family of Apocynaceae, which has wider medicinal activities such brain tonic, anti-epileptic, anti-mania and anti-oxidant. The current predictive study was aimed to know pharmacokinetics and drug likeness of selected phytochemicals present in *T.divaricata* by using online tool Swiss-ADME. **Methods:** The air-dried leaves were pulverized and subjected to Soxhlet extraction and percolation using the solvents, namely, ethanol, hydroalcoholic solvent (50:50 and 70:30 ethanol: water) and water to obtain four different extracts. Aqueous extract was made through percolation. Subsequently, gas chromatography-mass spectrometry was used to analyze each extract further. All the bioactive compounds were subjected to *in silico* ADME and drug-likeness studies and the finalized compounds were undergone cell cytotoxicity activity. **Results:** All the four extracts have distinct physicochemical properties linked to the chemicals naturally present in large amounts in *T. divaricata* leaves. The compound 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) indolizine having good drug likeness of 4.50 and 3.50 respectively and good lipophilicity which has the log P value of 2.51 and 3.73 appropriately. IC_{50} values of compounds were found to be 312.1 ± 0.2µg/ml for 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 393.7 ± 0.2µg/ml for 2-(4-methylphenyl) indolizine. **Conclusion:** Major bioactive chemicals were found in the aqueous extract and based on the calculated ADME parameters they are anticipated to serve as cytotoxic lead compounds. It is advocated that current predictive results should be authenticated by *in vitro* and *in vivo* toxicological and pharmacological assay.

Key words: Apocyanceae, GC-MS analysis, *In silico* study, Cell cytotoxicity studies.

INTRODUCTION

Many cultures employ plants as medicine, and the pharmaceutical industry uses them as a source of many potent pharmaceuticals with significant biological and therapeutic applications.[1] Several phytochemicals, usually referred to as secondary metabolites, are found in plants. Due to their individual, additive, or synergistic effects on health, phytochemicals are helpful in the treatment of some illnesses.[2] Plants have been sources of effective medications throughout history and will continue to be crucial for screening novel lead compounds. Recognizing the biologically potent chemicals in plants, which leads to additional biological and pharmacological investigation, is a vital component of plant research.[3-5] An evergreen and precious ethnomedicinal plant, *Tabernaemontana divaricata Linn*., is used worldwide for various conventional treatments. In Asia, Australia, China's mangrove forests, Japan, and India, the plant is extensively dispersed.[6] *T.divaricata L*., also called "Nantyarvattam " locally, is a member of the Apocynaceae family of plants, which is widespread in India. It has significant therapeutic value in Ayurveda medicine due to its anthelmintic, antiinflammatory and diuretic properties.[7] Compounds exist in additional species of Tabernaemontana, revealing incredible biological activities. *T. divaricata* revealed powerful antiproliferative effects on the human epidermoid larynx carcinoma cell line (Hep 2);[8] furthermore, it remarkably suppressed cortical acetylcholinesterase activity and augmented neuronal activity in the cerebral cortex.[9] Due to the presence of similar active ingredients, plants belonging to the same genus may also display the same biological activity. Bioactive chemicals found in *T. divaricata* leaves have been identified. No published studies on gas chromatography-mass spectrometry (GC-MS) evaluation and insilico ADMET studies on the bioactive chemicals found in the various T. *divaricata* leaf extracts.

This study aimed to identify and analyze the bioactive substances in the various crude extracts of *T. divaricata* leaves.

MATERIALS AND METHODS

Plant sample

Fresh plant leaves of *T. divaricata* were collected from Kerala, India, on August 2-3, 2022. Botanist of Plant Anatomy Research Centre, Tambaram, Chennai, India, identified the sample of plant.

Extraction of crude extracts

It took around 14 days to air dry the plant's leaves at room temperature. The leaves were crushed and powdered after drying, and the samples were subjected to Soxhlet extraction using ethanol, hydroalcoholic solvent (50:50 and 70:30 ethanol: water) and water.[10] The extract was subsequently dried using Rotavapor.

The GC–MS analysis

Bioactive components from the several extracts of the leaves of *T. divaricata* were subjected to GC–MS

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analysis[11] using Shimadzu GC systems with QP2020 model equipped with SH-RXi-5Sil MS column (30 m in length × 0.25 mm in diameter × 0.25 um in thickness of film). An electron ionization system using high-energy electrons was used for the GC- MS spectroscopic detection (70 eV). As the carrier gas, pure helium gas (99.995% purity) was used at a 1.2 mL/min flow rate. A holding period of roughly 2 minutes was used with a starting temperature range of 50 to 150 ^{0}C. Finally, the temperature was increased to 280 ^{0}C. In a splitless mode, one microliter of the produced, 1%-diluted extracts with the appropriate solvents was injected. Based on the peak area created in the chromatogram, the relative quantity of the chemical components detected in each of the T. *divaricata* extracts was denoted as a percentage.

Identification of chemical constituents

Based on GC retention time on SH-RXi-5Sil MS column and matching of the spectra with computer software data of standards, bioactive chemicals isolated from various extracts of *T. divaricata* were detected.

In silico pharmacokinetics and drug-likeness

The structures of identified phytochemical constituents of the various extracts of *T. divaricata* leaves were obtained from NCBI PubChem Compound database (https://pubchem.ncbi.nlm.nih.gov/) in SMILES format, reconstructed and subjected to 3D structure optimization using ChemSketch software. The structures were saved in MOL format. File conversion from MOL format to PDB format was done using PyMoL v2.0.7. The ligands SMILES were used for *in silico* pharmacokinetics on Swiss ADME server[12] at default settings, to predicts the absorption, distribution, metabolism, and excretion (ADME) parameters and drug likeness.

MTT assay

HepG-2 cells (Liver cancer cells) were purchased from NCCS, Pune and were cultured in liquid medium (DMEM) supplemented 10% Fetal Bovine Serum (FBS), 100 µg/ml penicillin and 100 µg/ml streptomycin, and maintained under an atmosphere of 5% CO_2 at 37°C. The sample 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine were tested for *in vitro* cytotoxicity using HepG-2 cell line (Liver cancer cells).[13] Briefly, the cultured HepG-2 cells were harvested by trypsinization, pooled in a 15 ml tube. Then, the cells were plated at a density of 1×10^5 cells/ml cells/well (200 µl) into the 96-well tissue culture plate and treated with various concentrations of the sample in a serum free RPMI medium. Each sample was replicated three times and the cells were incubated at 37°C in a humidified 5% CO_2 incubator for 24 h. After the incubation period, MTT reagent (20 µl of 5 mg/ml) was added into each well and the cells incubated for another 2 h until purple precipitates were clearly visible under an inverted microscope. Finally, the medium together with MTT (220 µl) were aspirated off the wells and washed with 1× PBS (200 µl). Furthermore, to dissolve formazan crystals, DMSO (100 µl) was added and the plate was shaken for 5 min. The absorbance for each well was measured at 570 nm using a Microplate reader (Thermo Fisher Scientific, USA) and the percentage cell viability and IC_{50} value was calculated using AAT Bioquest tool (USA).

RESULTS AND DISCUSSION

Percentage yield

The average percentage yields of three batches of around 1 kg of air-dried powdered leaves were 3.7 % (SD = 0.23) of ethanol extract, 2.62% (SD = 0.05) of hydroalcoholic (70:30) extract, 1.46% (SD = 0.05) of hydroalcoholic (50:50) extract and 5.34% (SD = 0.22) of aqueous extract were obtained. The highest percentage yield was produced using aqueous extract. The majority of the components has polar properties.

Bioactive compounds turn up in the extracts

The bioactive components found in T. *divaricata* leaf extracts made from ethanol, hydroalcoholic, and aqueous solutions are displayed in Tables 1-4. On the basis of their sequence of elution in an SH-RXi-5Sil MS column, they were identified and described. Furthermore, provided were these bioactive substances' elution time, quantity and molecular formula. In regard to abundance, the principal three compounds present in the ethanolic extract were Phthalic acid, di(2-propyl pentyl) ester (67.96 %), 1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester (6.8 %) and Octadecane (4.29 %). The 70:30 hydroalcoholic crude extract contained 1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester (23.09 %) followed by 1,2-benzene dicarboxylic acid (9.84%) and Phthalic acid, cyclobutyl tridecyl ester (7.93%). The 50:50 hydroalcoholic crude extract had 1,2-benzene dicarboxylic acid (25.98%), Octane, 1-chloride- (14.33%) and 4,7-Dimethylundecane (11.47%) as the top three significant compounds. The aqueous crude extract contained 1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester (40.97%) followed by 1,2-benzenedicarboxylic acid, dioctyl ester (29.82%) and 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one (10.1%). The GC chromatograms of the four extracts flourished in Figures 1-4 exhibit the retention time in the column and the observed peaks that are related to the bioactive chemicals detected in the extract.

In-silico pharmacokinetics and drug-likeness

All the 27 compounds were identified from all extracts of *T. divaricata* leaf and all the compounds *in-silico* pharmacokinetics profile are shown in Table 5. The results suggest that many of the compounds are poorly soluble and have high gastrointestinal absorption (GIA), this include 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine; some are soluble with high GIA, could pervade blood-brain barrier (BBB) and not P-glycoprotein substrate. The compounds 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine having good drug likeness of 4.50 and 3.50 respectively and it having good lipophilicity which has the log P value of 2.51 and 3.73 appropriately.

MTT assay

The cytotoxicity of 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine were characterized by MTT assay method using HepG-2 cells (Liver cancer cells). The IC50 values were determined by the various concentrations of compounds and it was found to be 312.1 ± 0.2µg/ml for 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one (Fig 5) and 393.7 ± 0.2µg/ml for 2-(4-methylphenyl) Indolizine (Figure 6).

Several crude extracts were procured from the leaves of *T. divaricata* owing to Soxhlet extraction with solvents, namely, ethanol, 50:50 and 70:30 ethanol:water and water. GC–MS analysis of these extracts revealed the presence of various bioactive compounds. Phthalic acid (1,2-benzene dicarboxylic acid) and phthalic esters such as phthalic acid, di(2-propyl pentyl) ester; 1,2-benzene dicarboxylic acid, dioctyl ester; Di-isodecyl phthalate; Phthalic acid, cyclobutyl tridecyl ester; Phthalic acid, cyclohexylmethyl tridecyl ester are present in all the extracts but in different quantities. In addition, Octadecane is present in both ethanol and 50:50 ethanol:water extracts. According to investigations, GC-MS has shown several components that are biologically active chemicals. They have pharmacologic properties that have been demonstrated, and these properties may help the plant's capacity for healing. Phthalic esters were proven to exhibit antimicrobial, insecticidal anti-inflammatory effects.[14,15] 2-(4-methylphenyl) indolizine is present in the aqueous extract and the indolizine derivatives are reported to have antimicrobial, anticancer, antioxidant, anti-inflammatory, and anticonvulsant, enzymes inhibition activity as calcium entry blocker.[16-18] Pentadecane, Octadecane, Undecane, and decanoic acid

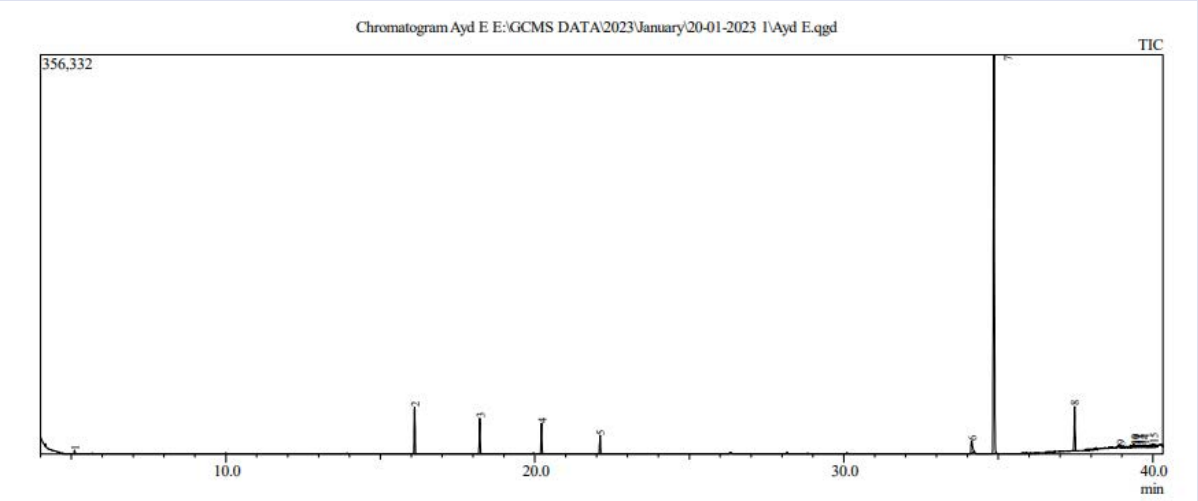

Figure 1: A typical chromatogram of the bioactive compounds present in ethanol crude extract

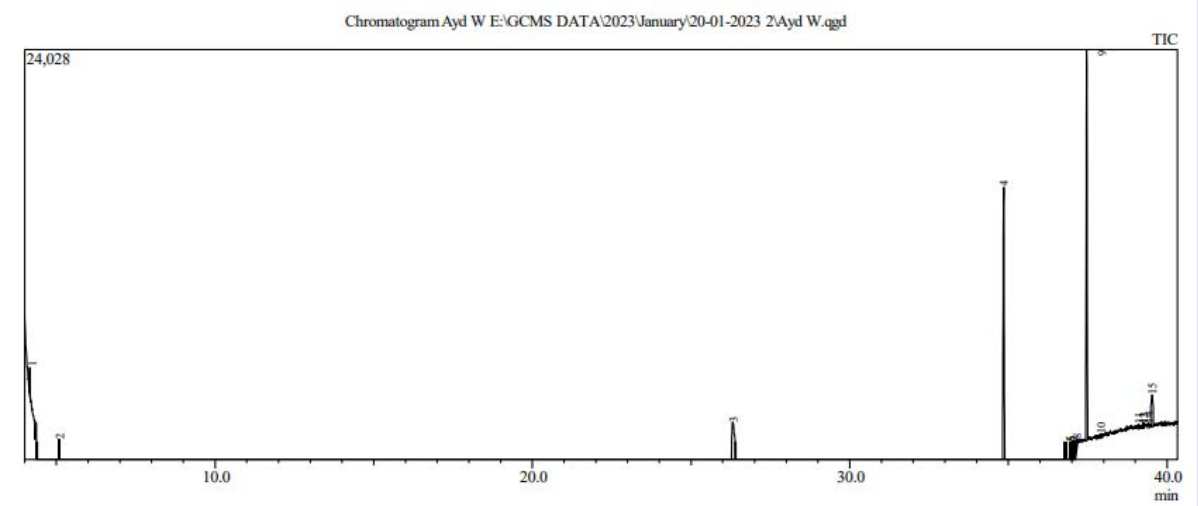

Figure 2: A typical chromatogram of the bioactive compounds present in aqueous crude extract

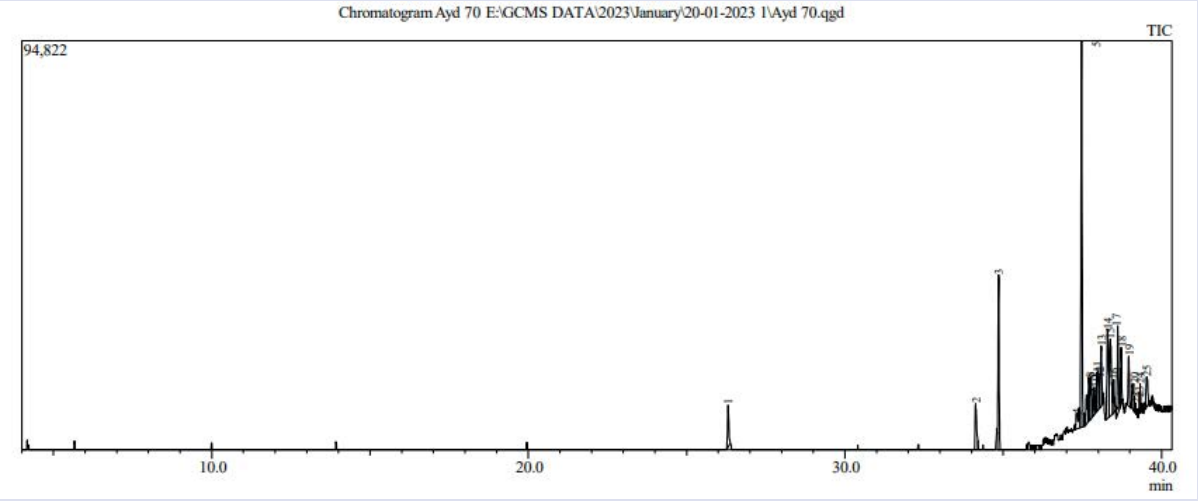

Figure 3: A typical chromatogram of the bioactive compounds present in 70:30 ethanol:water crude extract

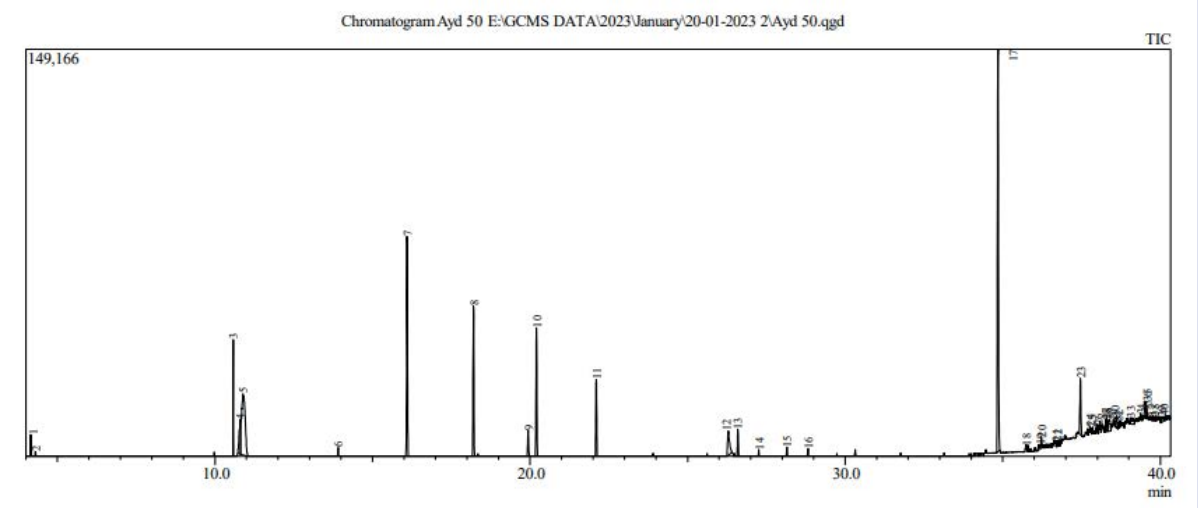

Figure 4: A typical chromatogram of the bioactive compounds presents in 50:50 ethanol: water crude extract

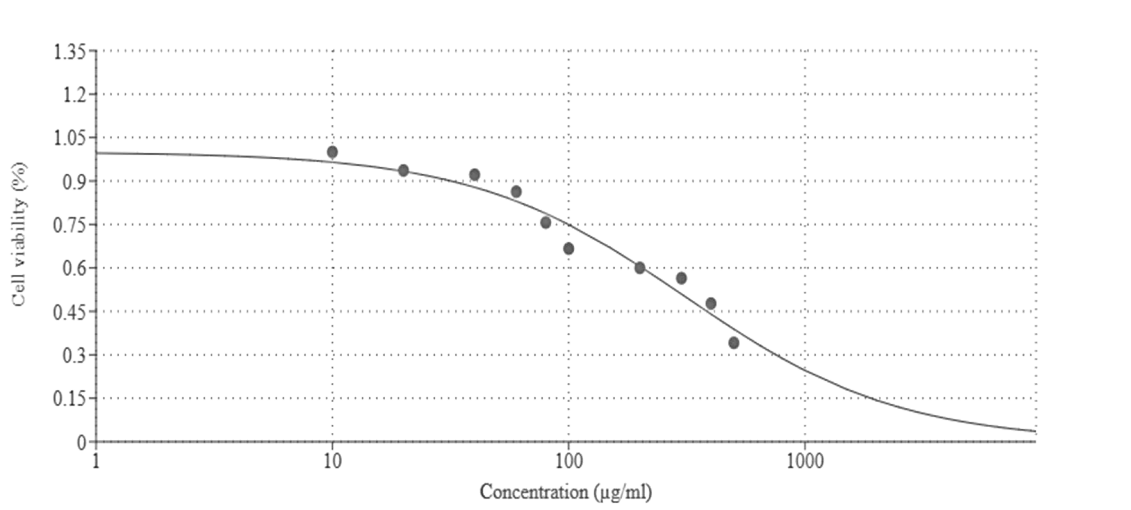

Figure 5: IC_{50} value for the compound 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one

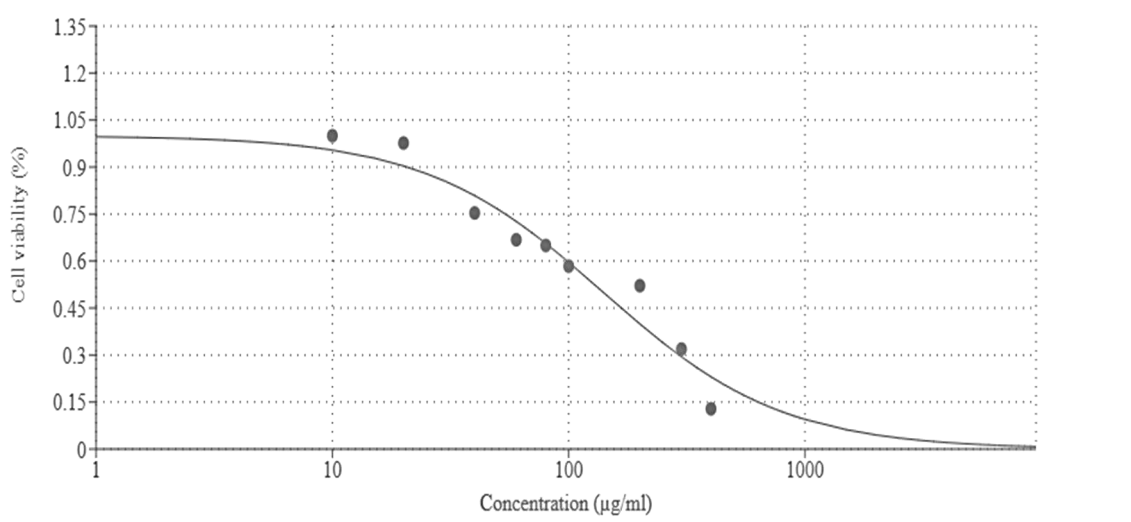

Figure 6: IC_{50} value for the compound 2-(4-methylphenyl) indolizine

Table 1: Biologically active chemical compounds of ethanol extract from *T. divaricata* leaves

Name of Compounds (Molecular formula)	Retention time (min)	%
Octadecane ($C_{18}H_{38}$)	20.22	4.29
2-[2-(benzoyloxy)ethoxy]ethyl benzoate ($C_{18}H_{18}O_5$)	34.14	3.15
Phthalic acid, di(2-propylpentyl) ester ($C_{26}H_{26}O_4$)	34.86	67.96
1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ($C_{24}H_{38}O_4$)	37.47	6.8

Table 2: Biologically active chemical compounds of aqueous extract from *T. divaricata* leaves

Name of Compounds (Molecular formula)	Retention time (min)	%
2-(Methylthio)ethanamine (C_3H_9NS)	4.16	1.47
1-bromoethyl benzene (C_8H_9Br)	5.09	1.15
4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one ($C_{11}H_{18}O_2$)	26.31	10.1
1,2-benzenedicarboxylic acid, dioctyl ester ($C_{24}H_{38}O_4$)	34.85	29.82
2-(4-methylphenyl) Indolizine ($C_{15}H_{13}N$)	37.02	4.05
1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ($C_{24}H_{38}O_4$)	37.47	40.97
2-(1,1,2,3,3,3-hexafluoropropyl) oxetane ($C_6H_6F_6O$)	39.53	6.51

Table 3: Biologically active chemical compounds of 70:30 (ethanol:water) extract from *T. divaricata* leaves

Name of Compounds (Molecular formula)	Retention time (min)	%
Benzoic acid, 3-amino-5-hydroxy-, methyl ester ($C_8H_9NO_3$)	26.30	3.03
2-phenyl-2,2'-bi-1,3-dioxolane ($C_{12}H_{14}O_4$)	34.13	3.98
1,2-benzenedicarboxylic acid ($C_8H_6O_4$)	34.86	9.84
6,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-3-one ($C_{12}H_{18}O$)	37.30	2.77
1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ($C_{24}H_{38}O_4$)	37.47	23.09
1-cyclopentene-1-carboxylic acid, 2-(chloromethyl)-, ethyl ester ($C_9H_{13}ClO_2$)	37.62	2.43
Di-isodecyl phthalate ($C_{28}H_{46}O_4$)	37.77	3.52
Phthalic acid, cyclobutyl tridecyl ester ($C_{25}H_{38}O_4$)	38.30	7.93
Phthalic acid, cyclohexylmethyl tridecyl ester ($C_{28}H_{44}O_4$)	39.11	2.19
6-(azidomethyl)-5-bromo-2-tert-butyl-4h-1,3-dioxin-4-one ($C_9H_{12}BrN_3O_3$)	39.33	1.15

Table 4: Biologically active chemical compounds of 50:50 (ethanol:water) extract from *T. divaricata* leaves

Name of Compounds (Molecular formula)	Retention time (min)	%
1,5-heptadiene, 7-deutero-3-methyl-, cis ($C_8H_{13}D$)	10.58	1.58
1-heptene, 3-methyl- (C_8H_{16})	10.81	3.07
Octane, 1-chloro- ($C_8H_{17}Cl$)	10.89	14.33
4,7-Dimethylundecane ($C_{13}H_{28}$)	16.10	11.47
Pentadecane ($C_{15}H_{32}$)	18.21	8.36
Octadecane ($C_{18}H_{38}$)	20.20	7.24
Undecane ($C_{11}H_{24}$)	22.10	4.3
Decanoic acid ($C_{10}H_{20}O_2$)	26.59	1.44
1,2-benzenedicarboxylic acid ($C_8H_6O_4$)	34.85	25.98
1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ($C_{24}H_{38}O_4$)	37.46	3.52

were proven to possess antimicrobial, antifungal, anti-inflammatory and antiproliferative activity.[19-22] 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one, Oxetane-containing compounds possess antineoplastic, antiviral (*arbovirus*), and antifungal activity.[23] 1,3-dioxolanes were proven to exhibit antibacterial and antifungal agents.[24] Out of all the compounds, 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine having significant drug likeness values. Based on the *in-silico* studies, the compounds 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine were subjected to cancer cytotoxicity studies. These compounds IC50 values were calculated by MTT assay using HepG-2 cells and it has IC_{50} value of 312.1 ± 0.2µg/ml for 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 393.7 ± 0.2µg/ml for 2-(4-methylphenyl) Indolizine.

CONCLUSION

This work showed that 4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one and 2-(4-methylphenyl) Indolizine are the two most active constituents of leaves extract of *T. divaricata* and these compounds have cytotoxicity activity on liver cancer. Thus, *T. divaricata* plant extract is a potential anti-cancer medicinal plant, and further *in vivo* and *in vitro* studies are required to validate the results of the study; and also promote *T. divaricata* active compounds optimization AND its clinical evaluations.

CONFLICTS OF INTEREST DECLARATION

We formally declare that we have no conflicts of interest.

Table 5: *In silco* ADME and drug-likeness parameters.

S.No	Identified compound	PubChem Code	Predicted ADME Parameters									
			Physicochemical properties			Lipophilicity	Water solubility		Pharmacokinetics			Drug-likeness
			MW (g/mol)	MR	TPSA (Å²)	LoP	ESOL Log S	ESOL class	GIB	BBB	P-gp	BS
1	Octadecane ($C_{18}H_{38}$)	11635	254.5	88.64	0.00	7.18	-6.33	Poorly soluble	Low	No	No	0.55
2	2-[2-(benzoyloxy)ethoxy]ethyl benzoate ($C_{18}H_{18}O_5$)	8437	314.33	84.03	61.83	3.14	-3.65	Soluble	High	Yes	No	0.55
3	Phthalic acid, di(2-propylpentyl) ester ($C_{26}H_{26}O_4$)	191964	390.56	116.30	52.60	6.16	-6.06	Poorly soluble	High	No	No	0.55
4	1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ($C_{24}H_{38}O_4$)	22932	390.56	116.30	52.60	6.27	-6.60	Poorly soluble	High	No	Yes	0.55
5	2-(Methylthio)ethanamine (C_3H_9NS)	34697	91.18	26.83	51.32	0.39	-0.24	Very soluble	High	No	No	0.55
6	1-bromoethyl benzene (C_8H_9Br)	12217727	185.06	44.09	0.00	2.87	.-3.22	Soluble	low	Yes	No	0.55
7	4,4,7a-Trimethylhexahydro-1-benzofuran-2(3H)-one ($C_{11}H_{18}O_2$)	536454	182.26	51.83	26.30	2.51	-2.58	Soluble	High	Yes	No	4.50
8	1,2-benzenedicarboxylic acid, dioctyl ester ($C_{24}H_{38}O_4$)	8346	390.6	116.30	52.60	6.30	-6.34	Poorly soluble	High	No	No	0.55
9	2-(4-methylphenyl) Indolizine ($C_{15}H_{13}N$)-	346948	207.27	67.80	4.41	3.73	-4.88	Moderately soluble	High	Yes	No	3.50
10	1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester ($C_{24}H_{38}O_4$)	22932	390.56	116.30	52.60	6.27	-6.06	Poorly soluble	High	No	Yes	0.55
11	2-(1,1,2,3,3,3-hexafluoropropyl) oxetane ($C_6H_6F_6O$)	1345997	208.10	30.31	9.23	2.87	-2.49	Soluble	High	Yes	No	0.55
12	Benzoic acid, 3-amino-5-hydroxy-, methyl ester ($C_8H_9NO_3$)	12438277	167.16	44.15	72.55	0.89	-1.84	Very soluble	High	No	No	0.55
13	2-phenyl-2,2'-bi-1,3-dioxolane ($C_{12}H_{14}O_4$)	569868	222.24	55.44	36.92	1.59	-1.87	Very soluble	High	Yes	Yes	0.55
14	1,2-benzenedicarboxylic acid ($C_8H_6O_4$)	1017	166.13	40.36	74.60	0.84	-1.57	Very soluble	High	No	No	0.85
15	6,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-3-one ($C_{12}H_{18}O$)	15215227	178.27	55.04	17.07	2.73	-2.39	Soluble	High	Yes	No	0.55
16	Di-isodecyl phthalate ($C_{28}H_{46}O_4$)	33599	446.7	135.53	52.60	7.73	-7.53	Poorly soluble	low	No	No	0.55
17	Phthalic acid, cyclobutyl tridecyl ester ($C_{25}H_{38}O_4$)	6423428	402.6	118.99	52.60	6.32	-5.83	Moderately soluble	low	No	Yes	0.55
18	Phthalic acid, cyclohexylmethyl tridecyl ester ($C_{28}H_{44}O_4$)	6423433	444.6	133.41	52.60	7.25	-6.93	Poorly soluble	low	No	Yes	0.55
19	6-(azidomethyl)-5-bromo-2-tert-butyl-4h-1,3-dioxin-4-one ($C_9H_{12}BrN_3O_3$)	546493	290.11	57.59	85.28	2.20	-3.82	Soluble	High	No	No	0.56
20	1-heptene, 3-methyl- (C_8H_{16})	20946	112.21	40.10	0.00	3.21	-2.68	Soluble	low	Yes	No	0.55
21	Octane, 1-chloro- ($C_8H_{17}Cl$)	8148	148.67	45.37	0.00	3.61	-4.42	Moderately soluble	low	Yes	No	0.55
22	4,7-Dimethylundecane ($C_{13}H_{28}$)	519389	184.36	64.60	0.00	5.16	-4.66	Moderately soluble	low	No	No	0.55
23	Pentadecane ($C_{15}H_{32}$)	12391	212.41	74.22	0.00	6.06	-5.24	Moderately soluble	low	No	No	0.55
24	Octadecane ($C_{18}H_{38}$)	11635	254.5	88.64	0.00	7.18	-6.33	Poorly soluble	low	No	No	0.55
25	Undecane ($C_{11}H_{24}$)	14257	156.31	54.99	0.00	4.56	-3.78	Soluble	low	Yes	No	0.55
26	Decanoic acid ($C_{10}H_{20}O_2$)	2969	172.26	51.96	37.30	3.00	-2.96	Soluble	High	Yes	No	0.85
27	1,2-benzenedicarboxylic acid ($C_8H_6O_4$)	1017	166.13	40.36	74.60	0.84	-1.57	Very soluble	High	No	No	0.85

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