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GC-MS Profiling of Phytobioconstituents Present in *Andrographis paniculata* (Burm.f.) Nees Extract and Pharmacokinetic and Toxicity Properties by ADME/Tox Analysis

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Andrographis paniculata, commonly known as the "King of Bitters" has traditionally been used as a medicinal herb. The metabolite composition of *A. paniculata* is generally determined by its properties, which may be influenced by a range of factors, one of which is the part of the plant extracted. The objective of this research is to identify and characterize the putative metabolite composition in *n*-hexane extract of stem and leaf using gas chromatography-mass spectrometry. A total of 22 different phytobioconstituents were identified, including flavonoids, terpenoids, fatty acids, phenolic acids, quinones, alkaloids and vitamin. The pharmacokinetic properties of the identified phytobioconstituents, like drug-likeness and toxicity, were also predicted by ADME/Tox analysis. Phytobioconstituents, predicted to be drug-like can be further investigated as ligands by using *in silico* docking approaches, for disease targets. The study provides empirical evidence for future study that might lead to their therapeutic applications and industrial product development.

Keywords: GC-MS Profiling, Phytobioconstituents, *Andrographis paniculata*.

INTRODUCTION

Andrographis paniculata (Burm.f.) Nees is a traditional medicinal herb in India, Pakistan, China and other Asian countries [1,2]. It's been used in the treatment of fever, upper respiratory infections, acute bacillary dysentery, snake bites, insect bite diabetes, and malaria for a long time [3,4]. Pharmacological studies show that *A. paniculata* has a wide variety of pharmacological activities, including anti-inflammatory [5], antiviral [6], antibacterial [7], anticancer [8], hepatoprotective, hypertension [9,10] and platelet aggregation inhibition [11]. The pharmaceutical industry is now dealing with significant attrition rates of preclinical and clinical candidates due to toxicity or a lack of optimal pharmacokinetic properties, resulting in expensive and longer timelines for drug development [12]. Currently, the physical and chemical analyses available for evaluating the quality of *A. paniculata* are typically done separately, which is inadequate. Furthermore, there is a lack of relevant analytical data for assessing the consistency of commercial *A. paniculata* quality. The purpose of this study is to investigate and analyze the chemical constituents of *A. paniculata*. *A. paniculata* was extracted in hexane solvent and then analyzed by using gas chromatography coupled with mass spectrometry (GC-MS) for the identification of phytobioconstituents. *A. paniculata*'s key bioactives can be used as important assets in the pharmaceutical and nutraceutical sectors. To be effective as a drug, the compound must reach its target in the body in a bioactive state and stay there until the predicted biological activities occur. One of the most common reasons for discontinuing drug research is poor pharmacokinetic properties. Compounds with good oral bioavailability, low or no toxicity and optimal levels of physico-chemical characteristics are critical factors for drug development [13,14]. Drug development starts with the assessment of absorption, distribution, metabolism, excretion (ADME) and toxicity (Tox) initially in the discovery process, when there are many compounds to analyze. The pharmacokinetic or drug-likeness properties, as well as the toxicity of compounds from *A. paniculata* acquired from gas chromatography-mass spectrometry analysis, were virtually determined using ADME/Tox analysis.

EXPERIMENTAL

Procurement and verification of plant materials: Leaves from approximately 0.3-0.5 m tall *Andrographis paniculata* herb were collected from the garden of Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. (25.272º N,82.998º E). After authentication, a voucher of the specimen (DG/21-22/354) was deposited in the herbarium of the Faculty of Aurveda, Institute of Medical Sciences, Banaras Hindu University, Varansi, India.

Chemicals: Analytical standard solvents supplied by Merck were used for extraction in the study.

Extraction of plant material: Leaves of *A. paniculata* were rinsed thoroughly, dried at room temperature in the shade and then crushed with a mixer grinder. In the Soxhlet extractor, 100 g of powdered material was employed for 32 h with 300 mL of *n*-hexane as solvent. The light green extract was filtered and evaporated to dry at 45 ºC using a rotatory evaporator and stored in a sealed jar at -40 ºC for future use.

GC-MS analysis: The GC-MS technique was used to investigate *n*-hexane extract of *A. paniculata* (HEAP). The Shimadzu QP-2010 Ultra GC-MS instrument has a capillary standard and a non-polar column of 60 M TRX 5-MS (Dimension: 30 m, ID: 0.25 mm, film: 0.25 mm). The vehicle gas was helium, and the mobile phase flow rate was fixed at 1.21 mL min^{-1}. The temperature of the device's oven was raised from 60 to 280 ºC at a rate of 10 ºC/min and the injection volume was set at 2 µL. The electron ionization energy system was carried out at 70 eV. A flow time of 60 min was employed. The sample was completely dissolved in hexane and run at a range of 40-650 *m/z*. The results were recorded and subsequently evaluated and equated using the Wiley spectral library search database. The mass spectra were obtained over a period of 45 min. The comparative percentage of each compound was estimated by equating its average peak area to the total area, while parameters necessary to determine compound classification such as molecular weight, molecular formula structure of the active metabolites of the test sample with its name were corroborated.

ADME/Tox analysis: Absorption, distribution, metabolism, excretion and toxicity (ADMET) of compounds identified by GC-MS, were predicted using online computational tools. The pkCSM-pharmacokinetics web tool (http://structure.bioc.cam.ac.uk/pkcsm) uses graph-based signatures and experimental data to predict and optimize small-molecule ADME/Tox properties [15]. The molecular structures of the compounds were entered into the ADME/Tox online tools pkCSM-pharmacokinetics using the simplified molecular-input line-entry specification (SMILES) nomenclature.

RESULTS AND DISCUSSION

Analysis of bioactive compounds: The extraction of plant material and subsequent analysis are critical steps in the development of herbal products because it assure accuracy and quality control. The current study used GC-MS to identify the biologically active chemicals present in the *n*-hexane extract of *A. paniculata* (HEAP). The results indicated the presence of a range of bioactive compounds comprising fatty acids, vitamins, terpenoids, steroids, ketone, ester, and different types of alkane compounds.

The GC-MS chromatograms represented the 32 retention peaks and 22 different kinds of phytochemicals present in HEAP (Fig. 1). However, in a study, 29 peaks and only 12 compounds were identified in the methanolic extract of *A. paniculata* [16]. Whereas Roy *et al*. [17] reported a total of 25 retention peaks and 27 compounds were recognized by GC-MS in chloroform solvent extract. Retention time, area of the peak, concentration, molecular formula, compound nature, molecular structure and CAS numbers are presented in Table-1.

ADME/Tox analysis: The compounds identified by GC-MS analysis were employed in the Pkcsm tool [18] to scrutinized

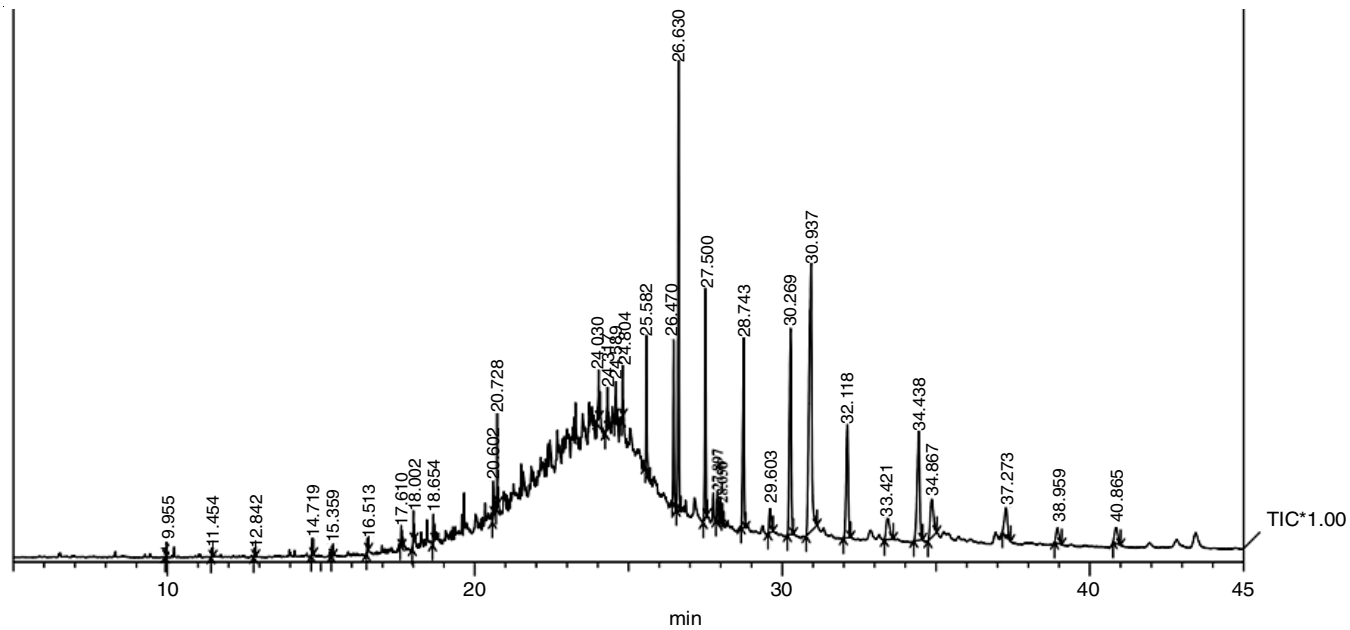

Fig. 1. GC-MS analysis of herbal extract using hexene solvent *A. paniculata* extract

TABLE-1
COMPOUND PRESENT IN N-HEXANE EXTRACT OF *A. paniculata* BY USING GS-MS ANALYSIS

Retention time	Area	Area (%)	Compounds	m.f.	Nature of compound	Cas No.
9.955	263116	0.11	Dodecane	$C_{12}H_{26}$	Alkane	112-40-3
12.842	386252	0.16	Hexadecane	$C_{16}H_{34}$	Alkane	544-76-3
14.719	863408	0.35	2(4*H*)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	$C_{11}H_{16}O_2$	Terpene	17092-92-1
15.359	402404	0.16	Tetradecane	$C_{14}H_{30}$	Alkane	629-59-4
16.513	672705	0.27	Pentadecane	$C_{15}H_{32}$	Alkane	629-62-9
17.610	789808	0.32	Octadecane	$C_{18}H_{38}$	Alkane	593-45-3
18.002	1428739	0.58	Neophytadiene	$C_{20}H_{38}$	Diterpene	504-96-1
18.654	1387631	0.56	Nonadecane	$C_{19}H_{40}$	Alkane	629-92-5
20.728	4530322	1.84	Phytol	$C_{20}H_{40}O$	Diterpenoid	150-86-7
24.030	2637289	1.07	Heneicosane	$C_{21}H_{44}$	Alkane	629-94-7
24.317	3478364	1.41	1,2-Benzenedicarboxylic acid, dinonyl este	$C_{26}H_{42}O_4$	Ester	84-76-4
24.589	2227294	0.90	(2,3-Diphenylcyclo-propyl)methyl phenyl sulfoxide, *trans*-	$C_{22}H_{20}OS$	Sulfoxide	131758-71-9
24.804	1982481	0.80	Hexacosane	$C_{26}H_{54}$	Alkane	630-01-3
26.630	33609071	13.65	Squalene	$C_{30}H_{50}$	Triterpene	111-02-4
27.897	2461497	1.00	Oxirane, 2,2-dimethyl-3-(3,7,12,16,20-pentamethyl-3,7,11,	$C_{30}H_{50}O$	Triterpenoid	7200-26-2
28.050	894429	0.36	Hexadeca-2,6,10,14-tetraen-1-ol, 3,7,11,16-tetramethyl-	$C_{20}H_{34}O$	Diterpenoid	7614-21-3
29.603	3144940	1.28	γ-Tocopherol	$C_{28}H_{48}O_2$	Isoprenoid	7616-22-0
30.269	24495848	9.95	Tetracontane	$C_{40}H_{82}$	Alkane	4181-95-7
30.937	47700639	19.37	α-Tocopherol	$C_{29}H_{50}O_2$	Vitamin E	59-02-9
33.421	4947322	2.01	Stigmasterol	$C_{29}H_{48}O$	Steroid	83-48-7
34.867	8210310	3.33	γ-Sitosterol	$C_{29}H_{50}O$	Phytosterols	83-47-6
38.959	2982936	1.21	Octadecanal	$C_{18}H_{36}O$	Long chain fatty aldehyde	638-66-4

Lipinski's rule, absorption, distribution, metabolism, excretion, and toxicity. Each rule is based on a threshold value for the attributes. This web tool includes a description of the method design, information on method validation and information on the datasets used for most methods in the literature [18]. The results are shown in Tables 2-5. According to Lipinski's rule any compound must follow at least 3 conditions out of five rules. These are as follow: molecular weight: ≤ 500, number of hydrogen bond: ≤ 5, number of hydrogen bond accepter: ≤ 10, number of hydrogen bond donor: ≤ 5, molecular refractivity:

TABLE-2
PHARMACOPHORE PROPERTIES OF SELECTED COMPOUNDS FROM HEXANE EXTRACT OF *A. paniculata*

Compounds	Molecule properties					
	m.w. (g/mol)	Log P	#Rotatable bonds	#Acceptors	#Donors	Surface area (A^2)
Dodecane	170.34	4.9272	9	0	0	78.754
Hexadecane	226.448	6.4876	13	0	0	104.213
2(4*H*)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	180.247	2.4384	0	2	0	78.962
Tetradecane	198.394	5.7074	11	0	0	91.483
Pentadecane	212.421	6.0975	12	0	0	97.848
Octadecane	254.502	7.2678	15	0	0	116.943
Neophytadiene	278.524	7.1677	13	0	0	128.294
Nonadecane	268.529	7.6579	16	0	0	123.308
Phytol	296.539	6.3641	13	1	1	133.778
Heneicosane	296.583	8.4381	18	0	0	136.038
1,2-Benzenedicarboxylic acid, dinonyl este	418.618	7.5014	18	4	0	183.28
(2,3-Diphenylcyclopropyl)methyl phenyl sulfoxide, *trans*-	332.468	4.9916	5	1	0	145.374
Hexacosane	366.718	10.3886	23	0	0	167.863
Squalene	410.73	10.605	15	0	0	189.185
Oxirane, 2,2-dimethyl-3-(3,7,12,16,20-pentamethyl-3,7,11,	426.729	9.8162	15	1	0	193.982
Hexadeca-2,6,10,14-tetraen-1-ol, 3,7,11,16-tetramethyl-	290.491	6.1244	10	1	1	131.709
γ-Tocopherol	416.69	8.53184	12	2	1	186.362
Tetracontane	563.096	15.85	37	0	0	256.972
Vitamin E	430.717	8.84026	12	2	1	192.727
Stigmasterol	412.702	7.8008	5	1	1	186.349
γ-Sitosterol	414.718	8.0248	6	1	1	187.039
Octadecanal	268.485	6.4468	16	1	0	121.105

TABLE-3
ABSORPTION AND DISTRIBUTION OF COMPOUNDS IDENTIFIED FROM GCMS ANALYSIS OF HEXENE EXTRACT OF *A. paniculata*

Compounds	Water solubility	Caco2 permeability	Intestinal absorption (human)	Skin permeability	P-glycoprotein			VDss (human)	Fraction unbound (human)	BBB permeability	CNS permeability
					Substrate	I inhibitor	II inhibitor				
Dodecane	-6.673	1.378	92.42	-1.329	No	No	No	0.582	0.197	0.863	-1.635
Hexadecane	-8.131	1.375	91.046	-2.34	No	No	No	0.672	0.044	0.939	-1.417
2(4*H*)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	-2.38	1.618	97.255	-2.671	No	No	No	0.223	0.533	0.286	-2.812
Tetradecane	-7.528	1.376	91.733	-1.859	No	No	No	0.646	0.11	0.901	-1.526
Pentadecane	-7.861	1.376	91.389	-2.117	No	No	No	0.664	0.074	0.92	-1.471
Octadecane	-8.481	1.373	90.358	-2.644	No	No	No	0.661	0	0.977	-1.308
Neophytadiene	-8.559	1.425	92.85	-2.518	No	No	Yes	0.692	0	0.983	-1.299
Nonadecane	-8.565	1.372	90.015	-2.727	No	No	No	0.642	0	0.996	-1.253
Phytol	-7.554	1.515	90.71	-2.576	No	No	Yes	0.468	0	0.806	-1.563
Heneicosane	-8.558	1.37	89.328	-2.793	No	No	Yes	0.579	0	1.033	-1.144
1,2-Benzenedicarboxylic acid, dinonyl este	-6.656	1.372	90.187	-2.693	No	No	Yes	0.359	0	-0.313	-2.338
(2,3-Diphenyl-cyclopropyl)-methyl phenyl sulfoxide, *trans*-	-6.343	1.358	96.826	-2.698	Yes	Yes	Yes	0.264	0.04	0.898	-1.039
Hexacosane	-7.679	1.123	87.609	-2.756	No	No	Yes	0.312	0.008	1.128	-0.871
Squalene	-8.517	1.216	90.341	-2.768	No	No	Yes	0.411	0	0.981	-0.955
Oxirane, 2,2-dimethyl-3-(3,7,12,16,20-pentamethyl-3,7,11,	-8.447	1.176	91.045	-3.181	No	No	Yes	0.422	0	0.894	-1.464
Hexadeca-2,6,10,14-tetraen-1-ol, 3,7,11,16-tetramethyl-	-7.254	1.501	90.274	-2.345	No	No	No	0.427	0.029	0.715	-1.707
γ-Tocopherol	-7.602	1.458	90.043	-2.62	No	Yes	Yes	0.732	0	0.739	-1.669
Tetracontane	-3.715	1.061	82.799	-2.735	No	No	Yes	-0.439	0.266	1.392	-0.107
Vitamin E	-6.901	1.345	89.782	-2.683	No	No	Yes	0.709	0	0.876	-1.669
Stigmasterol	-6.682	1.213	94.97	-2.783	No	Yes	Yes	0.178	0	0.771	-1.652
γ-Sitosterol	-6.773	1.201	94.464	-2.783	No	Yes	Yes	0.193	0	0.781	-1.705
Octadecanal	-7.784	1.477	91.645	-2.732	No	No	No	0.481	0.034	0.856	-1.455

40-130. The results are shown in Table-2. Absorption was predicted by water solubility, Caco2 permeability, Intestinal absorption (human), Skin Permeability, P-glycoprotein substrate, P-glycoprotein-I inhibitor and P-glycoprotein-II inhibitor.

The water solubility of a compound reflects the solubility in water at 25 ºC. A compound's permeability in a human colorectal adenocarcinoma cell line (Caco2) is considered high if it has a predictive value greater than 0.90. All compounds were found to be highly permeable for Caco2 cells. Compound with an absorbance of < 30% value is considered to be poor Intestinal absorption (human). All the compounds were found to be high intestinal absorption. The compound is considered to have relatively low skin permeability if it has a log > -2.5. Among all of the 22 identified different phytobioconstituents compounds, dodecane, hexadecane, tetradecane, pentadecane and hexadeca-2,6,10,14-tetraen-1-ol, 3,7,11,16-tetramethyl were found to have relatively low skin permeability. Distribution was predicted by VDss (human), Fraction unbound (human), BBB permeability and CNS permeability. Uniformly distribution of the compound is considered low if logVDss < -0.15 and high if log VDss > 0.45. Tetracontane is the only compound, which has low distribution in tissue rather than blood plasma.

Efficacy of a compound in the bounded and unbounded state in the blood is predicted by Fu. For a compound, log BB > 0.3 considered to be readily cross the blood-brain barrier while log BB < -1 is poorly distributed to the brain. Compounds with log PS greater than -2 are thought to be able to enter the central nervous system (CNS), whereas compounds with log PS less than -3 are thought to be unable. Accept 2(4*H*)-benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl and 1,2-benzene dicarboxylic acid, all of these compounds can easily cross the blood-brain barrier and enter the CNS. Metabolism was predicted by CYP2D6 substrate, CYP3A4 substrate, CYP1A2 inhibitior, CYP2C19 inhibitior, CYP2C9 inhibitior, CYP2D6 inhibitior and CYP3A4 inhibitior. Cytochrome P450 is an important detoxification enzyme, which oxidizes the xenobiotics. The isoforms CYP2D6 and CYP3A4 metabolize if the compound

TABLE-4
METABOLISM AND EXCRETION OF COMPOUNDS IDENTIFIED FROM GCMS ANALYSIS OF HEXENE EXTRACT OF *A. paniculata*

Compounds	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitior	CYP2C19 inhibitior	CYP2C9 inhibitior	CYP2D6 inhibitior	CYP3A4 inhibitior	Total Clearance	Renal OCT2 substrate
Dodecane	No	No	No	No	No	No	No	1.696	No
Hexadecane	No	Yes	Yes	No	No	No	No	1.85	No
2(4*H*)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	No	No	No	No	No	No	No	1.051	No
Tetradecane	No	No	No	No	No	No	No	1.774	No
Pentadecane	No	Yes	Yes	No	No	No	No	1.811	No
Octadecane	No	Yes	Yes	No	No	No	No	1.924	No
Neophytadiene	No	Yes	Yes	No	No	No	No	1.764	No
Nonadecane	No	Yes	Yes	No	No	No	No	1.96	No
Phytol	No	Yes	Yes	No	No	No	No	1.686	No
Heneicosane	No	Yes	Yes	No	No	No	No	2.033	No
1,2-Benzenedicarboxylic acid, dinonyl este	No	Yes	No	No	No	No	No	2.024	No
(2,3-Diphenylcyclopropyl)methyl phenyl sulfoxide, *trans*-	No	Yes	Yes	Yes	Yes	No	No	0.24	No
Hexacosane	No	Yes	Yes	No	No	No	No	2.071	No
Squalene	No	Yes	No	No	No	No	No	1.791	No
Oxirane, 2,2-dimethyl-3-(3,7,12,16,20-pentamethyl-3,7,11,	No	Yes	No	No	No	No	No	1.396	No
Hexadeca-2,6,10,14-tetraen-1-ol, 3,7,11,16-tetramethyl-	No	Yes	Yes	No	No	No	No	1.886	No
γ-Tocopherol	No	Yes	No	No	No	No	No	0.821	No
Tetracontane	No	Yes	No	No	No	No	No	2.394	No
Vitamin E	No	Yes	No	Yes	No	No	No	0.794	No
Stigmasterol	**No**	Yes	No	No	No	No	No	0.618	No
γ-Sitosterol	No	Yes	No	No	No	No	No	0.628	No
Octadecanal	No	Yes	Yes	No	No	No	No	1.898	No

is predicted to be a substrate. Excretion was predicted by total hepatic and renal clearance to determine the dosing rate and Renal organic cation 2 (OCT2) substrate for renal deposition and clearance of compounds.

Toxicity was predicted by AMES toxicity, Max. tolerated dose (human), hERG I inhibitor, hERG II inhibitor, oral rat acute toxicity (LD_{50}), oral rat chronic toxicity (LOAEL), hepatotoxicity, skin sensitisation, *T. pyriformis* toxicity and Minnow toxicity. AMES test was predicted for mutageneic potential of the compounds. Maximum tolerance dose of a compound is low, if the minimum recommended tolerance dose (MDRD) is equal to or less than 0.477 log (mg/kg/day) and high if greater than 0.477 log (mg/kg/day). Of 22 identified compounds, 2(4*H*)-benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl, 1,2-benzene dicarboxylic acid, γ-tocopherol and vitamin cross the threshold of MDRD. Inhibitors of potassium channels encoded by hERG (human ether-a-go-go-gene) are the principal cause for of development of acquired log OT syndrome leading to fatal ventricular arrhythmia. LOAEL is predicted to identify the lowest dose that results in adverse effects observed. Prediction of hepatotoxicity is done for a compound that is associated with disrupted normal liver function. Skin sensitization is done for the dermally applied compounds. A compound with predicted value of more than -0.5 log μg/mL and less than log LC_{50} < -0.3 are regarded as toxic for *T. pyriformis* bacteria and minnow fish, respectively. Only 2(4*H*)-benzofuranone was found to be highly acute toxic for minnow fish whereas all compounds were toxic for *T. pyriformis* bacteria.

Conclusion

The therapeutic mechanism of a herb can be better implicit with an appropriate investigation of its bioactive secondary metabolites. *A. paniculata* tends to be an ideal source of phytochemicals and micronutrients that can be used to develop nutraceuticals and functional products. By using a GC-MS analytical approach, 22 compounds were identified. Further ADMET/Tox analysis discriminated between potential drugs and non-drugs. All compounds are predicted to have readily absorption and distribution on oral administration, except Tertracotane, which was found to fail to follow the Lipinski filter and has low distribution in tissue rather than blood plasma. Except, a terpene and an ester, all other compounds are predicted to have the potential to enter the central nervous system. Most compounds are predicted to be metabolized easily with no deposition in the kidney. Only 2,3-diphenyl-cyclopropyl)-methylphenyl sulfoxide has been identified as toxic to the liver. However, most compounds are found to have many bioactivities and relate to their applications in folklore medicine, but it requires more investigation for the development of novel or suitable drugs by allowing rapid design, assessment, and prioritization. It will encourage more natural drug formulation, safe products and improved production.

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TABLE-5
TOXICITY OF COMPOUNDS IDENTIFIED FROM GCMS ANALYSIS OF HEXENE EXTRACT OF *A. paniculata*

Compounds	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Oral rat acute toxicity (LD_{50})	Oral rat chronic toxicity (LOAEL)	Hepato-toxicity	Skin sensiti-zation	T. *pyriformis* toxicity	Minnow toxicity
Dodecane	No	0.324	No	No	1.566	1.45	No	Yes	1.898	-0.41
Hexadecane	No	0.141	No	No	1.521	1.307	No	Yes	1.825	-1.409
2(4*H*)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	No	0.641	No	No	2.018	1.935	No	Yes	0.022	1.499
Tetradecane	No	0.221	No	No	1.527	1.377	No	Yes	2.07	-0.927
Pentadecane	No	0.179	No	No	1.52	1.342	No	Yes	1.989	-1.168
Octadecane	No	0.066	No	Yes	1.544	1.241	No	Yes	1.37	-1.89
Neophytadiene	No	0.272	No	Yes	1.473	1.158	No	Yes	1.65	-2.039
Nonadecane	No	0.027	No	Yes	1.563	1.208	No	Yes	1.137	-2.131
Phytol	No	0.05	No	Yes	1.607	1.043	No	Yes	1.884	-1.504
Heneicosane	No	-0.057	No	Yes	1.611	1.146	No	Yes	0.748	-2.613
1,2-Benzenedicarboxylic acid, dinonyl este	No	1.094	No	Yes	1.245	2.883	No	No	0.512	-3.881
(2,3-Diphenylcyclopropyl)methyl phenyl sulfoxide, *trans*-	Yes	0.454	No	Yes	3.143	0.488	Yes	No	0.38	-0.561
Hexacosane	No	-0.251	No	Yes	1.74	0.997	No	Yes	0.337	-3.817
Squalene	No	-0.393	No	Yes	1.848	0.946	No	No	0.464	-3.485
Oxirane, 2,2-dimethyl-3-(3,7,12,16,20-pentamethyl-3,7,11,	No	-0.319	No	Yes	1.622	0.714	No	No	0.623	-3.029
Hexadeca-2,6,10,14-tetraen-1-ol, 3,7,11,16-tetramethyl-	No	-0.325	No	Yes	1.632	1.041	No	Yes	2.18	-0.889
γ-Tocopherol	No	0.781	No	Yes	2.21	2.052	No	No	0.946	-3.814
Tetracontane	No	0.172	No	Yes	2.174	0.58	No	Yes	0.285	-7.189
Vitamin E	No	0.775	No	Yes	2.072	1.987	No	No	1.017	-3.324
Stigmasterol	No	-0.664	No	Yes	2.54	0.872	No	No	0.433	-1.675
γ-Sitosterol	No	-0.621	No	Yes	2.552	0.855	No	No	0.43	-1.802
Octadecanal	No	-0.012	No	Yes	1.538	1.089	No	Yes	1.426	-1.679

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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