Computational Screening of Phytochemicals from Medicinal plants as COVID-19 Inhibitors

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ABSTRACT

Aggressive strategies are planned globally to combat the newly developed COVID-19 worldwide. This pandemic virus has spread and affected globally leading to an increase in death tolls. Currently, no effective drug for treatment and management of the disease is available. Nature has gifted us with valuable resources in the form of medicinal plants which are used since time immemorial for the treatment of various diseases. In this research a dataset of plant based bioactive compound was developed. A total of 101 phytochemicals were selected, virtually designed and its binding affinity with ACE enzyme was studied by molecular docking. Human ACE related carboxypeptidase and complex (PDB ID: 1R42) and (PDB ID: 6CS2) were selected for molecular docking studies as corona virus binds to ACE2 to enter into the host cell. Docking score results revealed that almost all selected phytochemicals binds to the pocket of the human ACE protein with high binding affinity and the scores were compared with chloroquine and hydroxychloroquine. The drug likeliness and ADMET analysis of all the screened compounds were performed. Two potential compound 6-α-acetoxygedunin and echitamine exhibited optimum binding with both the receptor.These phytochemicals can serve as lead molecule for further optimization and drug development against COVID-19. Therefore, it is predicted that the insights in the present study could be regarded valuable towards development of natural inhibitor of this virus.

Keywords: Molecular docking, phytochemicals, COVID-19, 6-α-acetoxygedunin, echitamine.

1. INTRODUCTION

The early episodes the novel coronavirus evolved in Wuhan, China, in December 2019 and later engulfed the whole world [1]. The World Health Organization announced the flare-up to be a public health emergency of international concern on 30 January 2020[2]. The COVID-19 is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes mild to severe respiratory tract infections [3].Although there is recovery of COVID-19 positive patients but still there is no authenticated medication to inhibit/kill this deadly virus. The disease is highly contagious and the longest watched span of viral shedding was for 37 days [4]. Patients suffered from multiple disorders with hypertension being the most widely recognized trailed by diabetes, heart problems and even multiple organ failure. SARS-CoV-2 is reported to utilise ACE-2 for entry into the target cells [5]. ACE 2, a protective protein widely distributed in human body is down regulated after viral infection, this decreases the degradation of angiotensin II and reduces production of angiotensin (1-7). Imbalance of these proteins in the RAS cascade leads to target organ damage [6].

The phytochemical from medicinal plants are used in the treatment of various diseases since ancient times. As compared to the synthetic drug(s) plant derived antiviral agents are associated with lesser side effects. Thus, phytochemicals may be a better alternative for the treatment of this dreaded pandemic disease. Bioactive phytochemicals like polyphenols, alkaloids, coumarins, saponins, flavonoids, terpenoids, limonoids, steroids, polysaccharides are found to inhibit genetically and functionally diverse viruses [7-9].

In this situation of great crisis due to the spread of the pandemic search for a drug to combat COVID-19 is need of the hour. *In-silico* techniques are inexpensive, fast and reliable methods in initial drug discovery and developments process. The objective of this study is to analyse the inhibitory action of bioactive molecules from medicinal plants on ACE-2 proteins by computational docking studies.

2. MATERIALS AND METHODS

2.1. Retrieval of Phytochemical ligands

A series of 3-D structures of different phytoconstituents obtained from phytochemical databases were virtually retrieved from NCBI Pubchem (https://pubchem.ncbi.nlm.nih.gov) in structure-data file (SDF) format and drawn by using Marvin Sketch and saved in .mol format in mol file. The mol file of the ligands was converted to PDBQT format using virtual autodocking software tool PyRx to obtain best atomic conformation of the ligands [10].

2.2. Retrieval of Protein

The 3-D X-ray crystalline structure of the two human ACE related protein with PDB ID:1R42; native human angiotensin converting enzyme-related carboxypeptidase (ACE-2)and PDB ID:6CS2;SARS

spike glycoprotein - human ACE-2 complex were obtained from RCSB protein data bank (https://www.rcsb.org/structure/1R42) and (https://www.rcsb.org/structure/6CS2) at atomic resolution 2.2Å and4.4Å respectively (**Figure 1**). The water, unwanted residues and chains were removed from the proteins using Notepad ++ 7.8.6 and further repaired using WHATIF server and saved in PDB format[11]. The 3-D ligplot graphs and 2-D interaction of the ligands and protein were generated using Discovery Studio 4.5. The binding site of the proteins was analysed using CASTp web server [12].

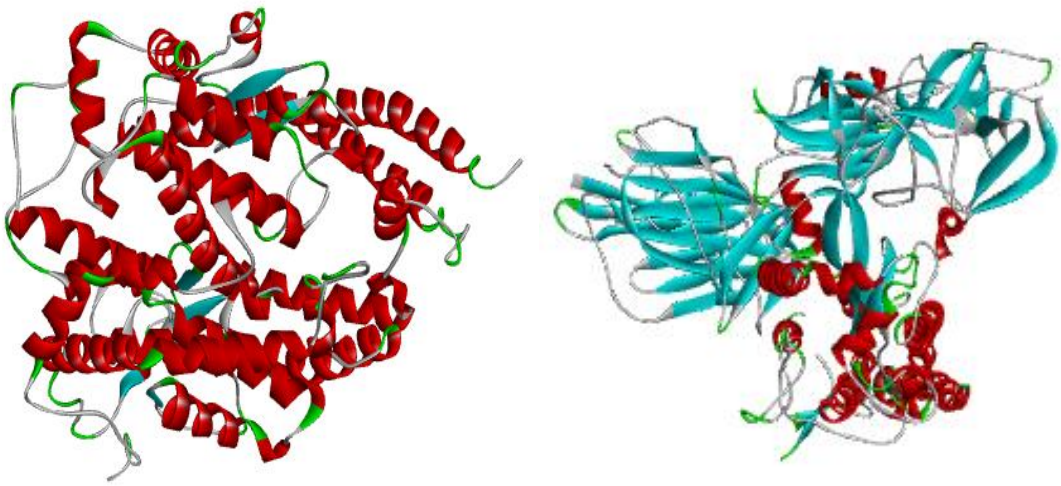


Figure 1. Native human ACE-2-related carboxypeptidase (PDB ID: 1R42) and SARS spike glycoprotein - human ACE-2 complex (PDB ID: 6CS2)

2.3. Molecular Docking

The molecular docking of the active site of the ACE-2 SARS protein with the selected series of phytochemicals was carried out in Autodock virtual docking software PyRx [13]. The ligands were retrieved in PyRx and protein 1R42 and 6CS2 were loaded in PDB format and converted in PDBQT format by water removal, hydrogen atom and kollman charges addition. The grid centre was positioned on the active site of the protein 1R42 and 6CS2. The grid value of 1R42 and 6CS2 for autogrid calculation were positioned at X=53.79, Y=60.55, Z=30.87 and X=161.014, Y=195.19, Z=190.43 respectively. The best binding affinity was selected from a set containing nine interacting poses after selection of the ligand and proteins in PDBQT format and running them in vina wizard simultaneously. The docking score of the virtually prepared phytochemicals with protein were compared with chloroquine and hydrochloroquine. The binding interactions of protein with selected candidate and type of interacting bond were analysed using Discovery Studio 4.5.

2.4. Drug-likeness and ADMET Prediction

The Lipinski rule of five signifies the drugability of the compound. This was calculated using Molinspiration tool https://www.molinspiration.com. The molecular weight, no of hydrogen bond donor and acceptor, no of Lipinski violations, no of rotatable bonds all were calculated. The ADMET calculations were performed using pkCSM [14] which produces the results based on graph-based signatures. Intestinal absorption, volume of distribution, blood brain barrier permeability, total clearance, LD 50 and mutagenicity were evaluated.

3. RESULTS AND DISCUSSIONS

Phytochemicals provide a strong root to the growing commercialization of medicines. Their biggest advantage is that they are nontoxic and rescue the body from any ailment with less or even no side effect. The use of phytochemicals for treatment of different diseases is an ancient concept. Many researches have proved that phytochemicals are less or even non-toxic and has been used to treat even life-threatening diseases [15]. A total of 101 phytochemicals belonging to various classes like alkaloids, glycosides, flavanoids, flavagline terpenes, terpenoids, lignan, tannins, phenols, coumarin, polysaccharides, resinoids and fatty acids were selected from databases and docked with human ACE-2 SARS protein.

3.1 Physicochemical and drug-likenessprediction

All the selected phytochemicals were virtually screened against Lipinski rule (RO5) using Molinspiration tool. The TPSA, no of hydrogen donor and acceptor, log P, molecular weight (MW), no of atoms and rotatable bonds for almost every candidate were within limits. The physicochemical derivative parameters are presented in **Table 1**.

Table 1. Physicochemical properties of selected phytochemical

Sr no.	Compounds	logp	TPSA	n	MW (≤500)	nON (≤10)	nOHNH (≤5)	nV	nrotb
1	Thalimonine	2.77	49.41	27	369.42	6	0	0	3
2	Indole	2.16	15.79	9	117.15	1	1	0	0
3	Cephaeline	3.33	63.20	34	466.62	6	2	0	6
4	Emetine	3.64	52.20	35	480.65	6	1	0	7
5	Psychotrine	4.40	63.53	34	464.61	6	1	0	6
6	Alangine	2.39	52.93	22	303.40	4	2	0	4
7	Tubulosine	4.86	69.75	35	475.63	6	3	0	5
8	Isotubulosine	4.86	69.75	35	475.63	6	3	0	5
9	Conessine	4.79	6.48	26	356.60	2	0	0	1
10	Deoxytubulosine	5.36	49.52	34	459.63	5	2	1	5
11	Ankorine	2.84	62.16	24	335.44	5	2	0	5
12	Conessidine	4.38	24.39	24	326.53	2	1	0	1
13	Quinazoline	1.54	25.78	10	130.15	2	0	0	0
14	Conimine	4.29	24.05	24	328.54	2	2	0	1
15	Isoconessimine	4.54	15.27	25	342.57	2	1	0	1
16	Kurchessine	5.47	6.48	27	372.64	2	0	1	3

17	Conessimine	4.54	15.27	25	342.57	2	1	0	1
18	Alamarine	1.21	84.59	25	338.36	6	2	0	2
19	holarrhimine	1.98	72.27	24	332.53	3	5	0	2
20	Senoterpine	0.53	33.12	11	149.19	2	1	0	0
21	Salsoline	1.36	41.49	14	193.25	3	2	0	1
22	9-demethylprotoe metinol	2.62	52.93	22	305.42	4	2	0	4
23	Bharatamine	2.62	32.70	21	281.36	3	1	0	1
24	Holafebrine	3.65	46.25	23	317.52	2	3	0	1
25	Aristololactum	3.73	60.56	22	293.28	5	1	0	1
26	Aristolic acid	3.68	65.00	22	296.28	5	1	0	2
27	Echitamine	-2.27	78.79	28	385.48	6	3	0	3
28	Picrinine	3.09	50.80	25	338.41	5	1	0	2
29	Akuammidine	2.84	65.56	26	352.43	5	2	0	3
30	Strictamine	3.38	41.91	24	322.41	4	0	0	2
31	Tetrahydroalstonine	3.41	54.57	26	352.43	5	1	0	2
32	Quinine	3.06	45.59	24	324.42	4	1	0	4
33	Cinchonidine	3.03	36.36	22	294.40	3	1	0	3
34	Dihydroconessine	4.97	6.48	26	358.61	2	0	0	1
35	Quercetin	1.68	131.35	22	302.24	7	5	0	1
36	Baicalin	0.55	187.12	32	446.36	11	6	2	4
37	Xanthohumol	4.80	86.99	26	354.40	5	3	0	6
38	Taxifolin	0.71	127.44	22	304.25	7	5	0	1
39	Epigallocatechin 3-gallate	2.25	197.36	33	458.38	11	8	2	4
40	Glucuronide	3.97	133.52	34	476.57	8	4	0	8
41	Ginkgetin	5.97	159.80	42	566.52	10	4	2	5
42	Tetrahydroxyflavano ne	0.80	107.22	21	288.25	6	4	0	1
43	Luteolin	1.97	111.12	21	286.24	6	4	0	1
44	leucodelphinidin	0.09	150.83	23	322.27	8	7	1	1
45	leucocyanidin	0.38	130.60	22	306.27	7	6	1	1
46	Decanoylphorb ol-13 acetate	5.88	130.37	40	560.73	8	3	2	13
47	Uvaol	6.91	40.46	32	442.73	2	2	1	1
48	Ursolic acid	6.79	57.53	33	456.71	3	2	1	1
49	Betulin	7.16	40.46	32	442.73	2	2	1	2
50	Linalool	3.21	20.23	11	154.25	1	1	0	4
51	Camphene	3.33	0	10	136.24	0	0	0	0
52	P-Cymene	3.90	0	10	134.22	0	0	0	1
53	6-α-Acetoxygedunin	4.13	121.65	39	540.61	9	0	1	5
54	Honokiol	5	40.46	20	266.34	2	2	1	5
55	SJP-L-5	3.47	57.24	24	329.35	6	0	0	5
56	Rhinacanthin E	4.07	98.78	32	442.42	9	0	0	9
57	Rhinacanthin F	3.95	98.78	32	444.44	9	0	0	10
58	Oleanane	8.86	0.00	30	412.75	0	0	1	2
59	Dammarenoic acid	8.08	57.53	33	458.73	3	2	1	8
60	Agastaquinone	2.96	80.67	25	340.38	5	1	0	2
61	Saikosaponins	1.98	207.99	55	780.99	13	8	3	6
62	Garciosaterpene A	8.11	63.60	36	498.75	4	1	1	7
63	Garciosaterpene C	7.23	54.37	33	454.69	3	1	1	5

64	Vaticinone	5.93	34.14	31	424.67	2	0	1	4
65	Betulinic Acid	7.04	57.53	33	456.71	3	2	1	2
66	Glycyrrhizin	1.97	267.04	58	822.94	16	8	3	7
67	Betulinaldehyde	7.62	37.30	32	440.71	2	1	1	2
68	Lupeol	8.29	20.23	31	426.73	1	1	1	1
69	β-amyrin acetate	8.55	26.30	34	468.77	2	0	1	2
70	Azulene	3.17	0	10	128.17	0	0	0	0
71	Eucalyptol	2.72	9.23	11	154.25	1	0	0	0
72	α-Curcumene	5.82	0	15	202.34	0	0	1	4
73	Elemol acetate	5.06	26.30	19	264.41	2	0	1	5
74	β -Eudesmol	4.01	20.23	16	222.37	1	1	0	1
75	Isololiolide	1.84	46.53	14	196.25	3	1	0	0
76	α-Spinasterol acetate	8.45	26.30	33	454.74	2	0	1	7
77	Cycloeucalenol	7.62	20.23	31	426.73	1	1	1	5
78	Cycloartenol	8.21	20.23	31	426.73	1	1	1	4
79	Oleuropeic acid	1.24	57.53	13	184.24	3	2	0	2
80	Madasiatic acid	4.96	97.98	35	488.71	5	4	0	1
81	Asiaticoside	0.37	315.21	67	959.13	19	12	3	10
82	Asiaticoside A	-0.55	335.44	68	975.13	20	13	3	10
83	Asiaticoside B	-0.61	335.44	68	975.13	20	13	3	10
84	Lupeol acetate	8.71	26.30	34	468.77	2	0	1	3
85	α-carotene	9.79	0	40	536.89	0	0	2	10
86	SennosideA	0.86	347.96	62	862.75	20	12	3	9
87	Silvestrol	2.92	171.85	47	654.66	13	4	2	11
88	Loliolide	1.84	46.53	14	196.25	3	1	0	0
90	Ellagic acid	0.09	141.33	22	302.19	8	4	0	0
91	Calanolide A	4.50	68.91	27	370.44	5	1	0	2
92	Hentriacontane	10.2	0	31	436.85	0	0	1	28
93	Linoleic acid	6.86	37.30	20	280.45	2	1	1	14
94	Oleic acid	7.58	37.30	20	282.47	2	1	1	15
95	Palmitic acid	7.06	37.30	18	256.43	2	1	1	14
96	Stearic acid	8.07	37.30	20	284.48	2	1	1	16
97	Behenic acid	9.13	37.30	24	340.59	2	1	1	20
98	Arachidic acid	8.37	37.30	22	312.54	2	1	1	18
99	Chrysin	2.94	70.67	19	254.24	4	2	0	1
100	Morin	1.88	131.35	22	302.24	7	5	0	1
101	α-D-Galacturonic acid	-2.77	127.44	13	194.14	7	5	0	1
102	Chloroquine	5	28.16	22	319.88	3	1	1	8
103	Hydroxy chloroquine	4	48.38	23	335.88	4	2	0	9

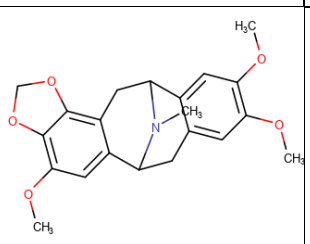
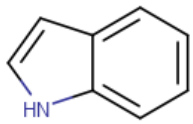
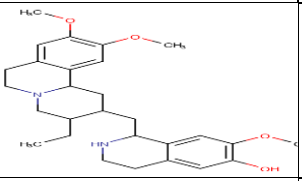
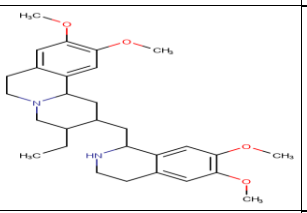
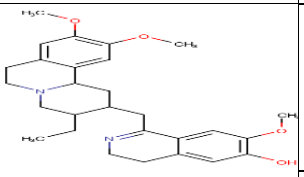
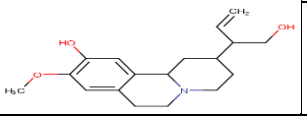
Log P: Partition coefficient; TPSA: Total Polar Surface Area; n: No of atoms; MW: Molecular weight; noN: No of hydrogen bond acceptor; nOHNH: No of hydrogen bond donor; nV: No of Violation; nrotb: No of rotatable bond.

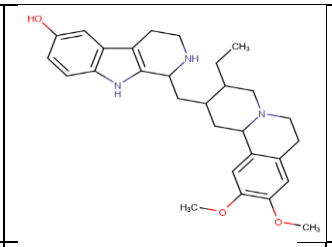
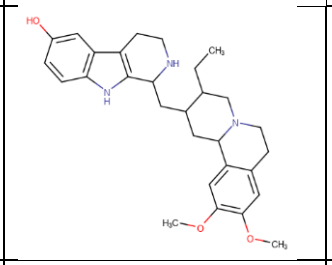
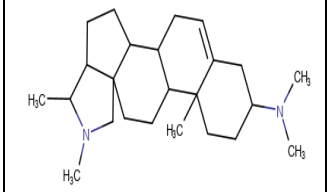
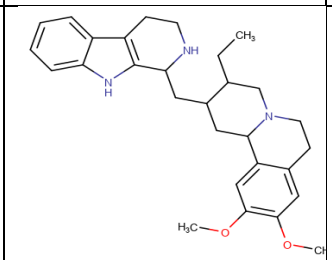
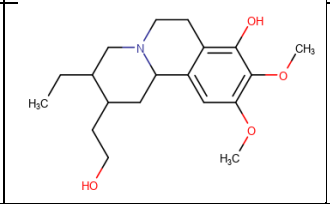
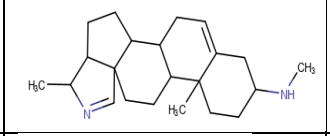
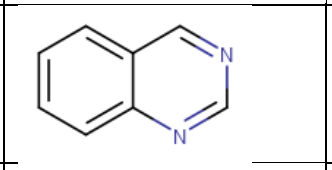
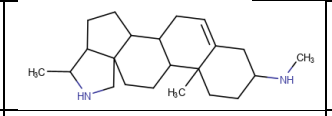
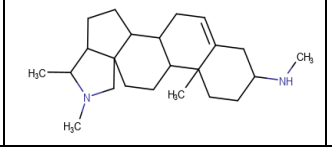
3.2. Molecular docking

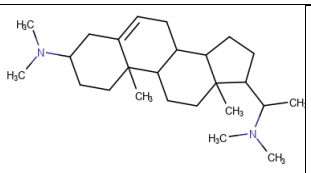
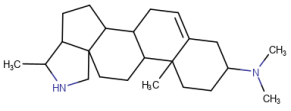
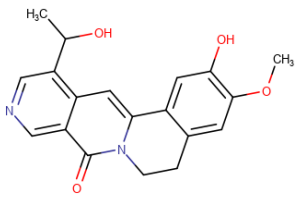
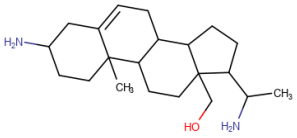
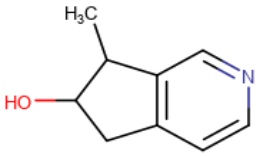
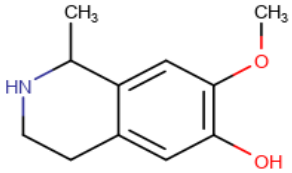
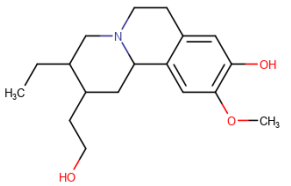
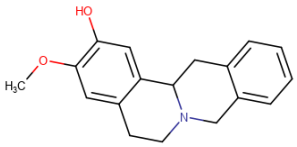
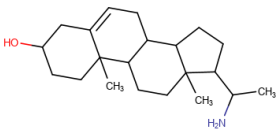
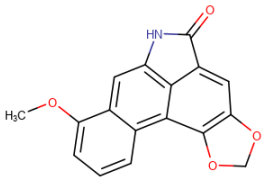
We docked all the selected phytochemical from the database with 1R42 and 6CS2. The docking score obtained ranges from -4.2 to -13.4 and -3.1 to -11.8 with 1R42 and 6CS2 respectively. Our study revealed that the best docking energy was exhibited by 6-α-acetoxygedunin with binding affinity of -

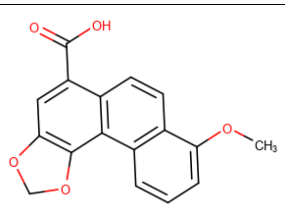
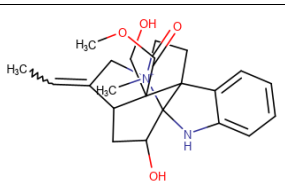
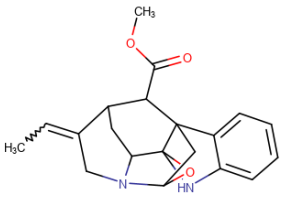
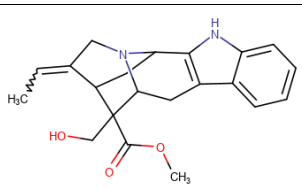
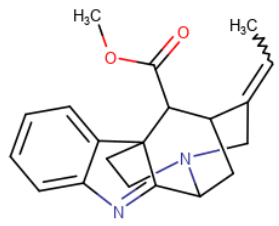
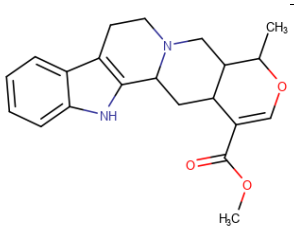
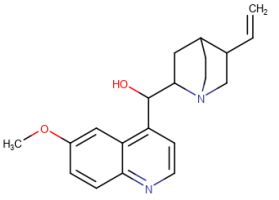
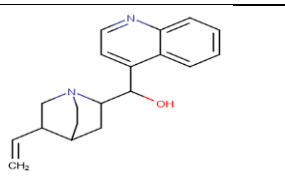
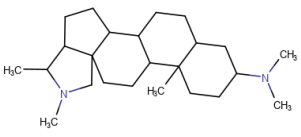
15.4 kcal/mol for 1R42 and -13.1kcal/mol for 6CS2 followed by echitamine (-12.1 kcal/mol for 1R42 and -10.3 kcal/mol for 6CS2). The 2-D structures of the phytochemicals and their docking score are enlisted in **Table 2**. 3-D binding and ligplot analysis of 6-α-acetoxygedunin with 1R42 and 6CS2 was carried out in Discovery Studio to predict the interacting amino acid binding site depicted in **Figure 2** and **Figure 3**. After molecular docking studies 6-α-acetoxygedunin was found bonded to the amino acid through conventional H bond: Tyr127, Pi-cation: Phe 504 and vanderwaal interactions: His 505, Try271, Asn 149, Leu 144 of 1R42 and vanderwaal interactions: Thr 51, Leu 52, Lys 291, Ser 292, Phe 293 of 6CS2.

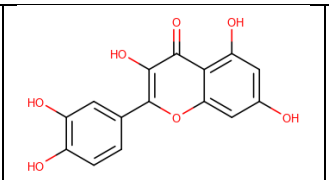
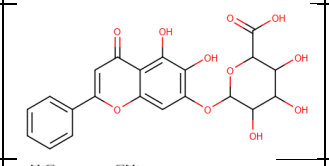
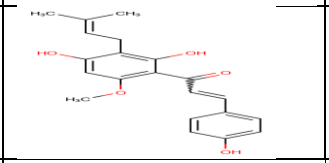
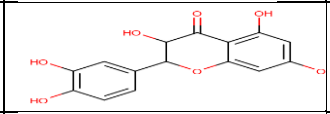
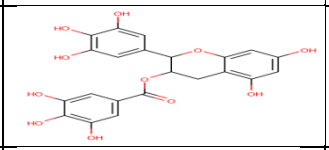
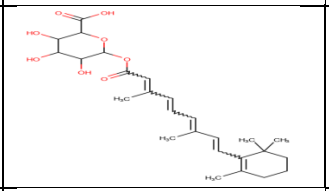
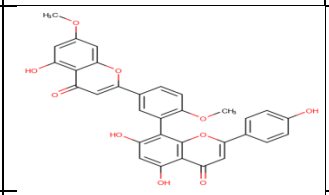
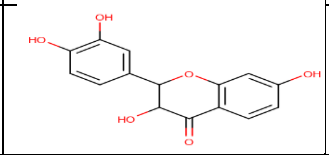
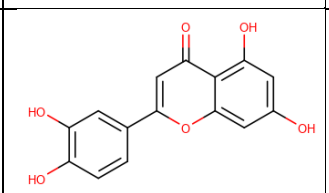
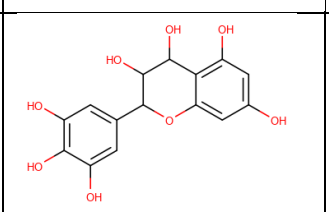
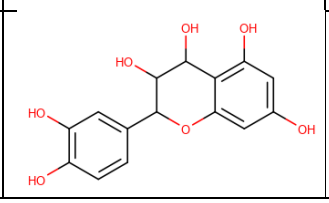
Table 2. 2-D structure and docking score of the phytochemicals

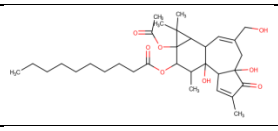
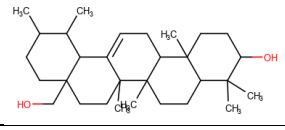
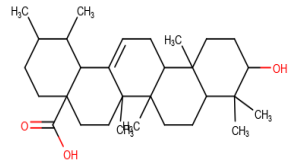
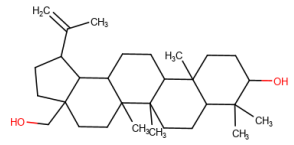
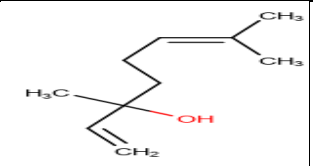
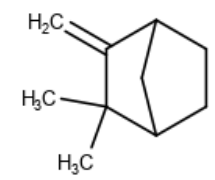
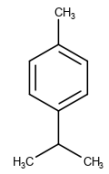
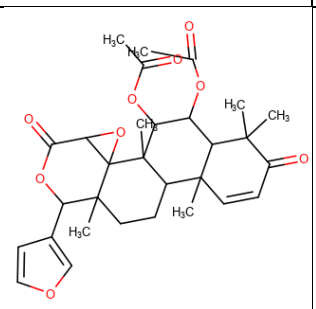
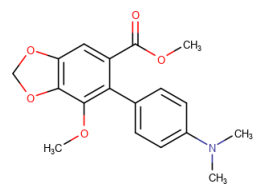
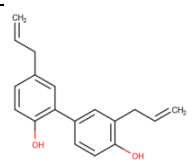
Class	**Sr no.**	**Compounds**	**Structure**	**CID**	**1R42**	**6CS2**
ALKALOIDS	1	Thalimonine		10893946	-6.5	-6.1
	2	Indole		798	-4.4	-3.9
	3	Cephaeline		442195	-7.3	-6.5
	4	Emetine		10219	-7.9	-5.6
	5	Psychotrine		65380	-8.0	-6.1
	6	Alangine		10851977	-6.1	-5.4

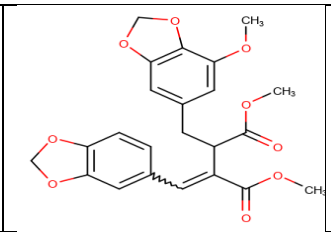
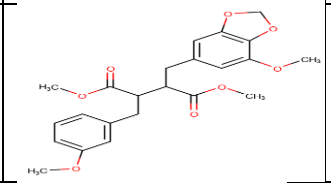
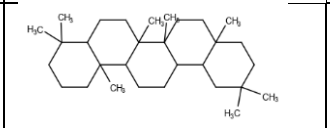
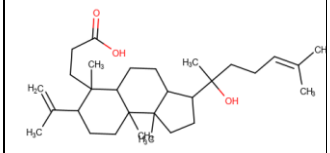
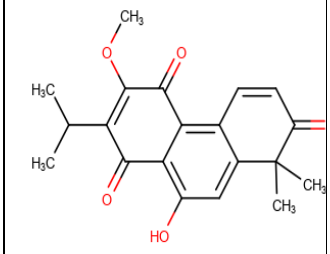
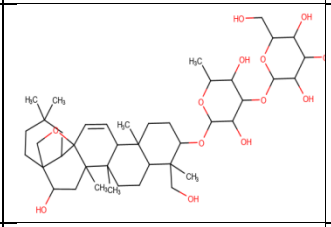
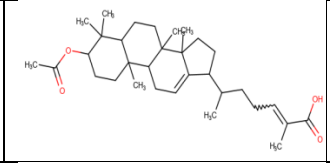
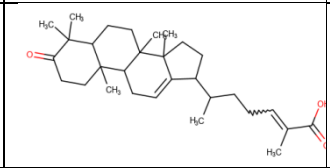
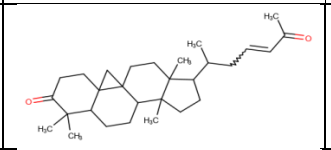
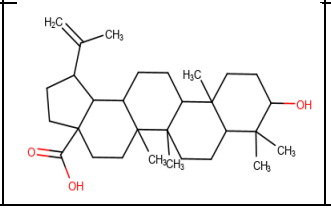
	7	Tubulosine		72341	-8.9	-6.8
	8	Isotubulosine		165327	-8.8	-6.8
	9	Conessine		441082	-7.5	-5.8
	10	Deoxytubulosine		165003	-8.2	-6.6
	11	Ankorine		442166	--5.9	-5.3
	12	Conessidine		22214027	-7.5	-6.0
	13	Quinazoline		9210	-4.6	-4.1
	14	Conimine		101686	-7.3	-6.0
	15	Isoconessimine		551434	-7.6	-5.9

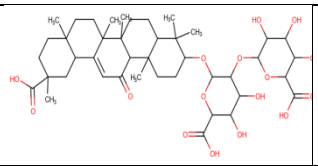
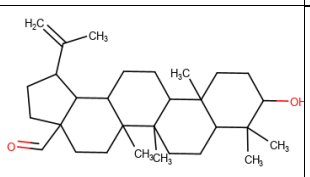
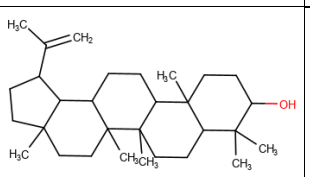
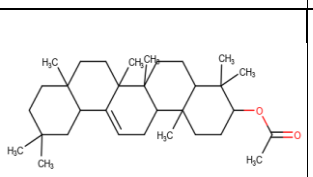
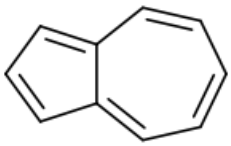
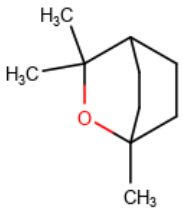
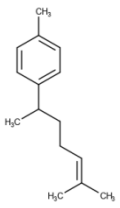
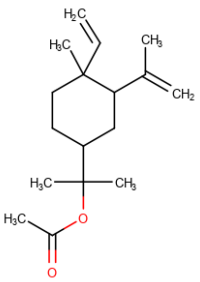
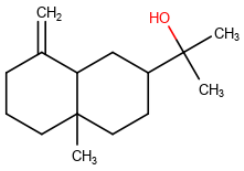
	16	Kurchessine		442979	-6.1	-5.0
	17	Conessimine		12303831	-7.8	-6.3
	18	Alamarine		442157	-6.8	-6.3
	19	Holarrhimine		15559632	-6.7	-5.7
	20	Venoterpine		56842090	-4.8	-4.5
	21	Salsoline		46695	-5.2	-4.6
	22	9-demethylprotoemetinol		158671	-6.2	-5.4
	23	Bharatamine		101946254	-6.7	-5.6
	24	Holafebrine		320374	-7.2	-5.5
	25	Aristololactum		96710	-6.9	-5.9

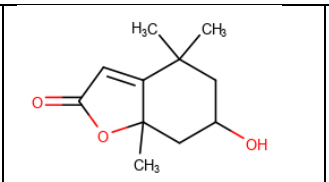
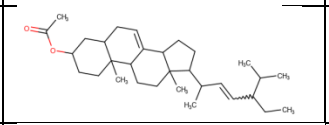
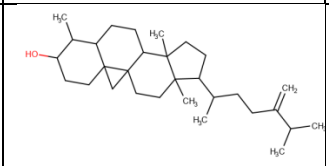
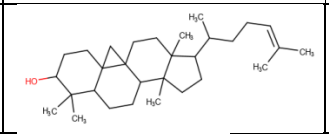
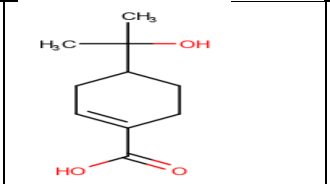
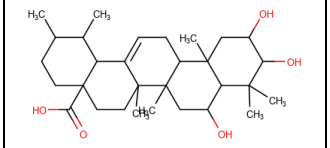
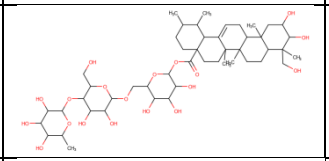
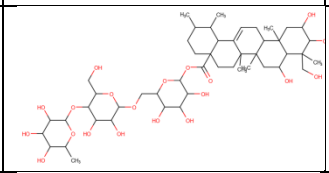
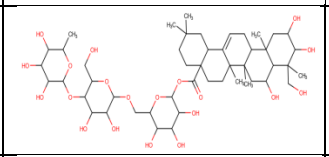
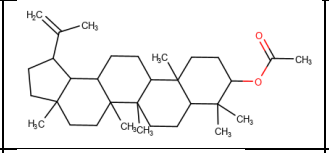
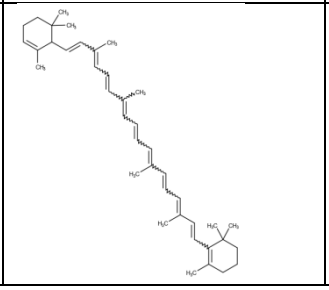
	26	Aristolic acid		119465	-7.3	-5.8
	27	Echitamine		11953926	-12.1	-10.3
	28	Picrinine		46229104	-7.2	-5.8
	29	Akuammidine		21160714	-6.9	-5.5
	30	Strictamine		301805	-6.9	-5.6
	31	Tetrahydroalstonine		72340	-7.3	-6.4
	32	Quinine		3034034	-6.8	-5.7
	33	Cinchonidine		90454	-6.5	-5.7
	34	Dihydroconessine		102093824	-7.1	-5.4

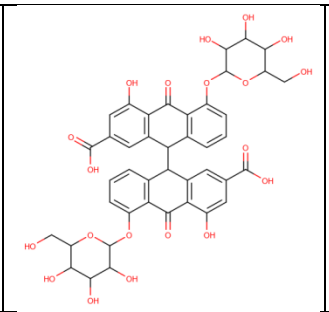
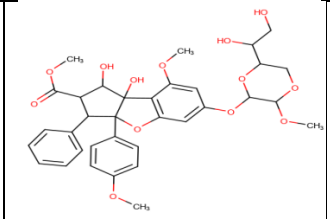
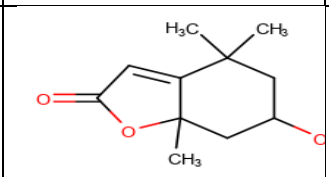
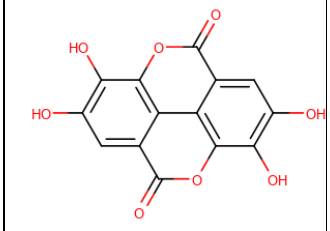
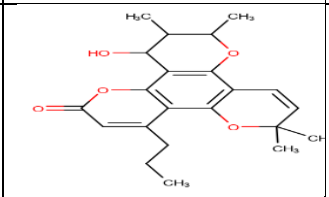
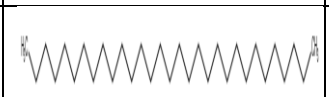
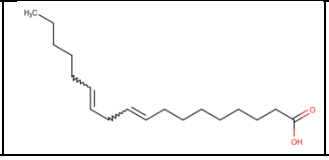
FLAVANOIDS	35	Quercetin		5280343	-7.1	-5.6
	36	Baicalin		64982	-7.6	-6.7
	37	Xanthohumol		639665	-6.8	-5.6
	38	Taxifolin		439533	-7.0	-5.6
	39	Epigallocatechin 3-gallate		65064	-7.9	-7.0
	40	Glucuronide		5281877	-7.6	-6.4
	41	Ginkgetin		5271805	-9.1	-7.3
	42	Tetrahydroxyflavanone		246330	-6.8	-5.5
	43	Luteolin		5280445	-6.9	-3.7
	44	Leucodelphinidin		3081374	-6.8	-5.7
	45	Leucocyanidin		71629	-7.0	-5.5

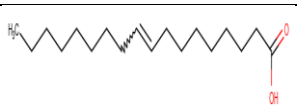
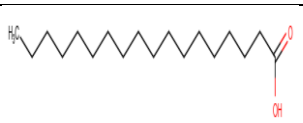
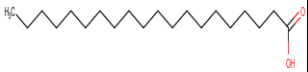
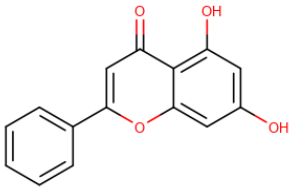
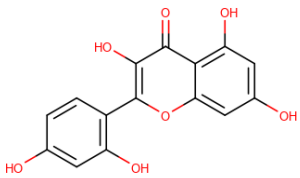
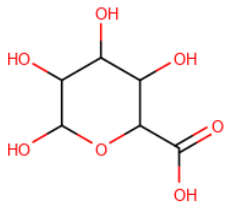
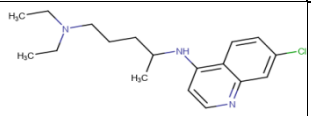
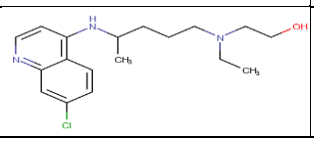
TERPENES	46	Decanoyl phorbol-13 acetate		9894037	-6.3	-5.7
	47	Uvaol		92802	-7.6	-6.2
	48	Ursolic acid		64945	-8.0	-6.7
	49	Betulin		72326	-7.5	-6.1
	50	Linalool		6549	-4.5	-3.7
	51	camphene		6616	-4.2	-3.7
	52	P-Cymene		7463	-4.8	-4.2
LIMONOIDS	53	6-α-acetoxygedunin		14485928	-15.4	-13.1
LIGNAN	54	SJP-L-5		53245967	-6.5	-4.8
	55	Honokiol		72303	-6.6	-5.5

	56	Rhinacanthin E		10366055	-6.3	-5.0
	57	Rhinacanthin F		10411189	-6.3	-5.8
TERPENOIDS	58	Oleanane		9548717	-8.1	-6.5
	59	Dammarenol acid		22215841	-7.3	-6.2
	60	Agastaquinone		177257	-7.2	-5.9
	61	Saikosaponins		107793	-8.9	-7.1
	62	Garciosaterpene A		6479439	-7.7	-6.7
	63	Garciosaterpene C		6479441	-7.6	-6.8
	64	Vaticinone		637226	-7.6	-6.1
	65	Betulinic Acid		64971	-7.5	-6.1

	66	Glycyrrhizin		14982	-9.3	-7.8
	67	Betulinaldehyde		99615	-7.4	-5.9
	68	Lupeol		259846	-8.1	-6.4
	69	β-amyrin acetate		92156	-8.3	-6.3
	70	Azulene		9231	-5.1	-4.6
	71	Eucalyptol		2758	-4.3	-4.1
	72	α-Curcumene		92139	-6.1	-4.6
	73	Elemol acetate		12978153	-5.6	-4.5
	74	β -Eudesmol		91457	-6.4	-5.0

	75	Isololiolide		11019783	-5.4	-4.7
	76	α-Spinasterol acetate		6452058	-7.5	-5.9
	77	Cycloeucalenol		101690	-7.1	-5.9
	78	Cycloartenol		500213	-7.9	-6.0
	79	Oleuropeic acid		188320	-5.2	-4.7
	80	Madasiatic acid		23132225	-7.6	-6.7
	81	Asiaticoside		11954171	-8.8	-7.0
	82	Asiaticoside A		45356919	-8.3	-6.7
	83	Asiaticoside B		91618002	-7.4	-7.7
	84	Lupeol acetate		92157	-8.1	-6.5
	85	α-carotene		6419725	-6.7	-5.9

GLYCOSIDE	86	Sennoside A		73111	-8.9	-8.0
FLAVAGLINE	87	Silvesterol		11787114	-7.1	-5.7
TANNIN	88	Loliolide		100332	-5.4	-4.9
PHENOLS	90	Ellagic acid		5281855	-6.9	-5.8
COUMARIN	91	Calanolide A		384854	-7.3	-5.8
RESINOIDS	92	Hentriacontane		12410	-4.6	-3.1
FATT	93	Linoleic acid		5280450	-5.0	-4.2

Y A C I D S	94	Oleic acid		445639	-4.4	-3.8
	95	Palmitic acid		985	-4.2	-3.7
	96	Stearic acid		5281	-4.4	-3.7
	97	Behenic acid		8215	-4.7	-3.7
	98	Arachidic acid		10467	-4.1	-3.7
F L A V O N O L S	99	Chrysin		5281607	-6.9	-5.3
	100	Morin		5281670	-6.8	-5.5
P O L Y S A C C H A R I D E	101	α-D-Galacturonic acid		445929	-5.2	-4.3
	102	Chloroquine		2719	-5.4	-4.6
	103	Hydroxychloroquine		3652	-5.7	-4.7

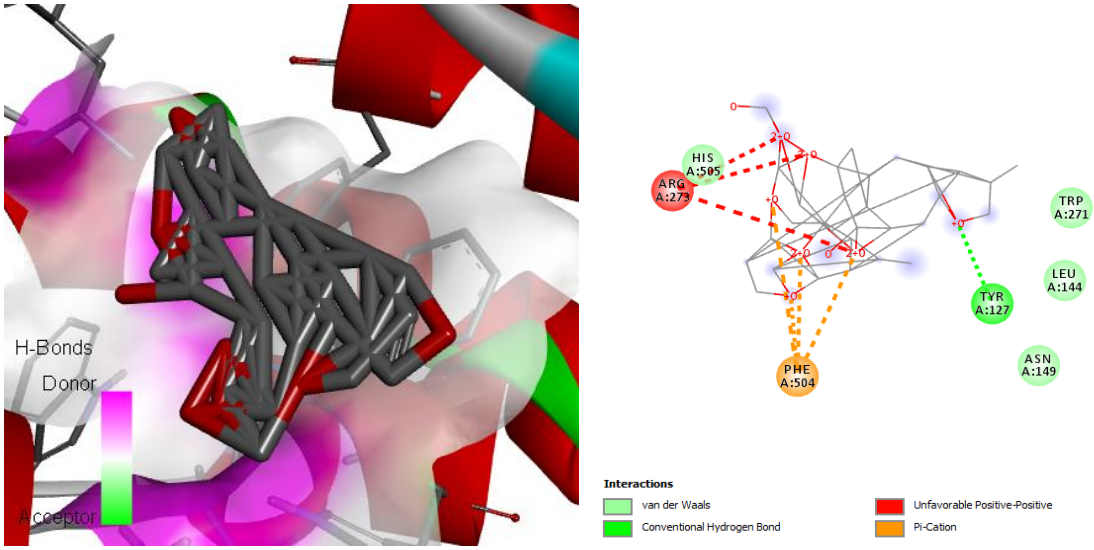


Figure 2. Binding interaction of 6-alpha-acetoxygedunin with 1R42

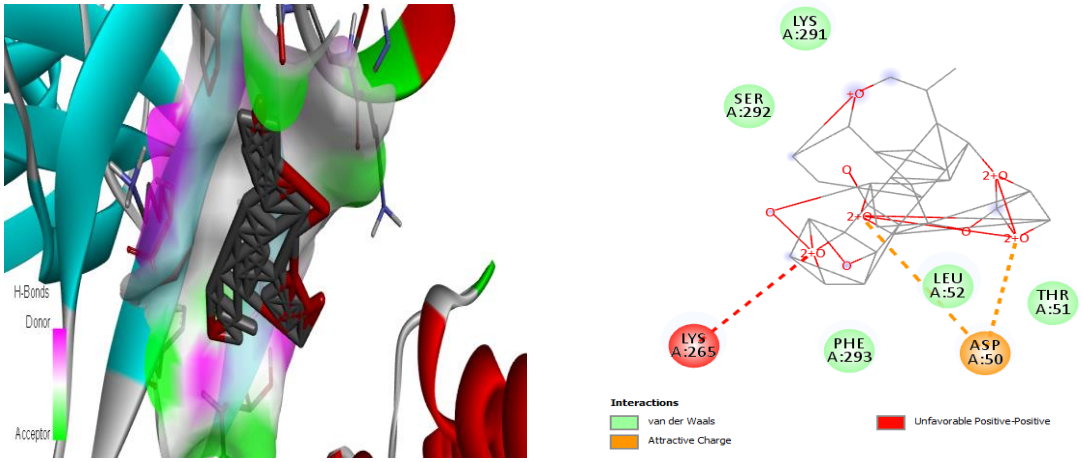


Figure 3. Binding interaction of 6-alpha-acetoxygedunin with 6CS2

3.3. Assessment of ADMET

The ADMET of the two selected candidate 6-α-acetoxygedunin and echitamine were assessed (**Table 3**). The absorption of both the selected candidates was more than 98% indicating good absorption characteristics. The volume of distribution is low therefore drug stays more time in plasma. Both 6-α-acetoxygedunin and echitamine are non-inhibitors of CYP isoenzymes (1A2, 2C19, 2C9, 2D6, 3A4) except 6-α-acetoxygedunin which is an inhibitor of 3A4. They are non-substrate of CYP2D6 and substrate of CYP3A4. Due to high lipophilicity both have low total renal clearance but these are non-transporters of renal OCT2 vital for drug disposition and renal excretion. They are non-mutagenic and non-carcinogenic as indicated by AMES toxicity test. 6-α-acetoxygedunin and echitamine have low LD50 score (3.529 and 3.302 respectively). Moreover, both these phytochemicals are very potent even in small dose.

Table 3. ADMET/ TOX Properties of 6-α-acetoxygedunin and echitamine.

Properties			6-α-acetoxygedunin	Echitamine
Absorption	IA (%)		100	98.138
Distribution	VDss(log L/kg)		0.115	0.789
	BBBP (Log BB)		-1.073	-0.212
Metabolism	CYP Inhibitor(Y/N)	1A2	N	N
		2C19	N	N
		2C9	N	N
		2D6	N	N
		3A4	Y	N
	CYP Substrate(Y/N)	2D6	N	N
		3A4	Y	Y
Excretion	Total clearance(log ml/ min/kg)		0.003	0.882
	ROS (Y/N)		N	N
Toxicity	AMES (Y/N)		N	N
	LD50 (mol/kg)		3.529	3.302

IA: Intestinal Absorption; VDss: Volume of distribution in human; BBB: Blood Brain Barrier permeability; TC:Total clearance; ROS: Renal Organic CationTransporter 2 Substrate.

4. CONCLUSION

ACE-2 inhibition plays a vital role in treatment against COVID -19 by blocking SARS coronavirus spike protein mediated cell fusion. 6-α-acetoxygedunin and echitamine exhibits lowest docking score thus have highest binding interactions with ACE-2 protein. On the whole, we conclude that the two phytochemicals 6-α-acetoxygedunin and echitamine have desired qualities to be a potent inhibitor of COVID -19. Thus, it is worth to carry out further investigations involving *in-vitro* and *in-vivo* studies on these molecules.

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CONFLICT OF INTERESTS

Authors declare no conflict of interest.

ABBREVIATIONS:

COVID-19: Coronavirus disease 2019; ADMET: Absorption, distribution, metabolism, excretion and toxicity; ACE: Angiotensin converting enzyme; RAS: Renin angiotensin system; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; OCT-2: Organic cation transporter 2.

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