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Phytochemical Screening of *Adathodai Kudineer* A Siddha Herbal concoction and Evaluation of its binding affinity with SARS-CoV-2 Spike Protein and ACE2 Receptor Spike protein Complex through Molecular Docking in silico approach

Research Article

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Abstract

Adathodai kudineer (AK) a Classical Siddha formulation is used to treat various fevers which cause moderate to severe acute respiratory symptoms as is indicated in the text. GC-MS analysis was carried out to identify the presence of potent lead molecules in *AK* against novel corona virus. The aqueous extract has shown the following bioactive compounds such as Napthalene, Benzene Propanol, Benzene Acetic Acid, Furazan-3-amine, Pyrazol-4-Carboxylic acid, 2(3H) Furanone. The ethanolic extract of *AK* exhibited the molecular compounds such as Eucalyptol, Toluene, 2-Carene, Alpha-Copaene, 1,6-Cyclodecadiene, Aromadendrene, Gamma-murolene, Beta-copaene, Cubebol, Selina-3,7 (11) - Diene, 2-Butanone. Molecular docking is a powerful approach in current trends to identify the possibility of pharmacological effects of medicinal compounds which could be exerted over their Corresponding Protein targets which are relevant for causing disease. Using Auto dock Vina Software, the biomolecules of *AK* were analyzed through molecular docking against SARS-CoV-2 Spike Protein (PDB ID 6LU7) and SARS-CoV-2 Spike Protein – ACE 2 receptor complex (6LZG). ADME properties were also recorded for the aqueous and ethanolic extracts of *AK* compounds using online tool SWISS ADME. The binding energy observed were of the order: -10.9 Kcal/mol, -8.0 Kcal/mol, -7.8 Kcal/mol for the compounds Alpha-Copaene, Gamma-Murolene, Selina-3,7 (11)–Diene respectively towards the protein target 6LZG and -8.2 Kcal/mol, -6.6 Kcal/Mol, -6.5 Kcal/Mol, for the compounds Alpha-Copaene, Cubebol, Aromadendrene respectively towards for the target 6LU7. These findings confirm that the Siddha formulation *Adathodai Kudineer* has some potent activity against SARS-CoV-2 Virus COVID19 disease.

Key Words: *Adathodai kudineer,* ADME, Siddha medicine, Protein–Protein Interaction, Molecular Docking, COVID 19.

Introduction

Emerging of Viral diseases like SARS, H1N1 influenza, MERS-CoV as epidemic in past decades. Now the current scenario in the entire world is facing a pandemic situation of Corona Viral infection which first emerges in Wuhan, China. World health organization declared the global health emergency due to COVID19 outbreak. The COVID 19, a disaster of 2020 has affected almost all the countries of the world with increasing death rates. As of 24 April 2021, there have been 145,216,414 confirmed cases of COVID-19, including 3,079,390 deaths, reported to WHO (1). It was identified that the Novel Beta Corona Virus named SARS-CoV2 is the causative organism behind the outbreak of COVD19.

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It is currently estimated that the incubation of SARS-CoV2 infection is between 2-14 days before the symptom's onset such as fever, cough, Sore Throat, dyspnea and the median disease incubation period was calculated as 5.1 days by the researchers of Johns Hopkins Bloomberg School of Public Health. The rapid transmission is occurred in COVID 19 is due to its person to person transmission is highly efficient and through respiratory droplets. The SARS-CoV2 is infecting the host cells by entering into the Human ACE 2 receptors through its enveloped spike glycoprotein (2). The primary target of the COVID 19 causing virus is the lung epithelial cells. The risk factors were assessed based on the available clinical data such as Hypertension, Cardiovascular Conditions, Cancer and Diabetes Mellitus.

Research Studies are being conducted to identify the impairment in response of antibody to SarsCoV2 infection, quantification of viral load, viral shedding prolongment in immunocompromised COVID 19 affected individuals. Immunity plays a significant role while challenging with viral infections. Some traditional Siddha medicines are being unique in treating viral infections at various stages including at the time of pathogenesis, prognosis due to its potent antiviral pharmacological

effects. Potent antiviral Siddha drug *Nilavembu kudineer* was documented as a wonderful therapeutic drug for the treatment of Chikungunya and dengue viral fever in both preclinical as well as clinical aspects(3)(4)(5). Likewise, identification of an antiviral drug with high therapeutic efficacy against COVID 19 infection is the urgent need in the current scenario because the medical world is only challenging and facing the disease using existing antiviral drugs which was identified for various other viral infections not exactly for SARS-CoV2.

Siddha system of medicines is a boon to human kind in treating various kind of infectious fever. According to Siddha pathology the disease COVID 19 is caused due to the elevation of *Kapha humour* while correlating its signs and symptoms. *Adathodai Kudineer* is a sastric Siddha medicine consists of various medicinal herbs was indicated to treat various fevers. *Adathodai kudineer* has been studied widely for its Anti pyretic and the individual ingredients seems to have multiple effects including Anti-Bacterial, Anti-fungal, Anti-Viral, Immuno Modulatory and much more (6). Since there is no proper drug was identified for the treatment of Corona Viral disease 19, the Siddha formulation *Adathodai Kudineer* have to be investigated for its Anti-corona Viral activity. Molecular docking analysis is an easiest and an effective way to identify the action potential of biomolecules of a drug against disease causing viral protein. GCMS was used to identify the presence of bioactive ingredients in *Siddha* drug *Adathodai Kudineer* and the minimum binding affinity of those biomolecules of KSK was found against Corona virus spike protein molecule and its ACE2 binding domain complex through molecular docking analysis. ADME properties was also evaluated for those compounds.

Materials and Methods

Source of drug

The Sastric drug *Adathodai Kudineer* was prepared as per the Siddha text *Siddha Vaithya Thirattu* (7) (8). The drug AK has the following 4 herbals such as *Adathodai* (*Justicia adhatoda L.*), *Adhimadhuram* (*Glycyrrhiza glabra L.*), *Thaalisapathiri* (*Taxus buccata L.*), *Arisi Thippili* (*Piper longum L.*).

GCMS analysis

GCMS analysis was carried out on the Aqueous and Ethanolic extract of Siddha drug *Kabasura kudineer* at the NABL accredited laboratory (Bureau veritas) in Chennai as per the standard protocol.

Protein preparation

TheSARS-CoV-2Virus main protease complex with an inhibitor N3 3D structure (PDBid: 6LU7) and Spike protein bound with ACE2 receptor protein molecule structure (PDBid:6LZG) was retrieved from the Protein Data Bank (PDB) and energy minimized and then converted into their respective PDBQT formats.2d. Ligand preparation:

The lead molecules were identified in the Siddha formulation achieved through GCMS analysis such as Napthalene, Benzene Propanol, Benzene Acetic Acid, Furazan-3-amine, Pyrazol-4-Carboxylic acid, 2(3H) Furanone, Eucalyptol, Toluene, 2-Carene, Alpha-Copaene, 1,6-cyclodecadiene, Aromadendrene, Gamma-murolene, Beta-copaene, Cubebol, Selina-3,7 (11) - Diene, 2-Butanone were selected as ligands for docking. 3D structures of the above mentioned selected ligands taken from PubChem structures and were minimized by applying Gnagstiere charge and coleman charge the root of the structure was detected torsion applied and the structures were saved in PDBQT format which is regularly used in Molecular docking analysis (9).

Molecular Docking

Molecular Docking analysis performed with a commonly well-known established software Auto dock Vina a very convenient and excellent screening tool for identifying binding energy between the 3D structures of each ligand and target proteins (10). Two target proteins PDB ID: 6LU7 and PDB ID: 6LZG were selected, a Grid-free docking performed, and the binding energies of each ligand found.

ADME properties prediction

The ADME (Adsorption, dissociation, Metabolism and excretion properties of above mentioned natural compounds predicted using Swiss ADME an online tool for ADME prediction (11).

Protein-Ligand interaction profile

Amino acids interactions of the ligands and their relation with the natural bonds were identified using a software tool Ligplot++(10). All the results were summarized and interpreted.

Results

Table 1. Phytocomponents Identified In The Aqueous Extract Of Medicinal Compound *AdathodaiKudineer*

S.No	RT	Area %	Library/ID (C\Database\NIST11.L)	Mol. F	Mol. W (g/mol)
1	12.430	24.69	Naphthalene	$C_{10}H_8$	128.169g/mol
2	12.989	18.34	Benzene Propanol	$C_9H_{12}O$	136.19 g/mol
3	12.989	18.34	Benzene Acetic Acid	$C_9H_{10}BrNO_2$	244.08 g/mol
4	24.257	13.93	Furazan-3-Amine	$C_2H_2N_4O_3$	130.06g/mol
5	25.238	14.07	Pyrazole-4-Carboxylic acid	$C_5H_6N_2O_2$	126.11g/mol
6	25.892	8.49	2(3H) Furanone	$C_4H_4O_2$	84.07g/mol

Fig 1.1 GCMS reading of Aqueous extract of *Adathodai Kudineer*

Fig 1.2 GCMS result of Ethanolic extract of *Adathodaikudineer*

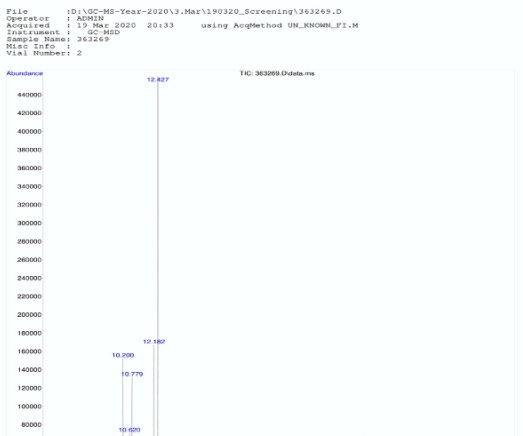


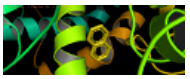
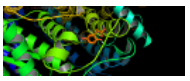
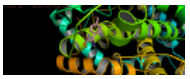
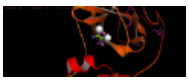
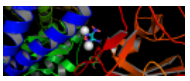
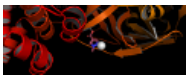
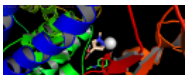
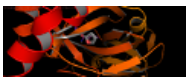
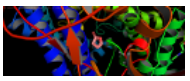
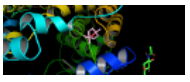
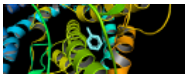
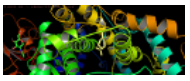
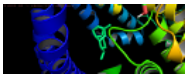
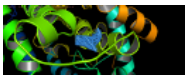
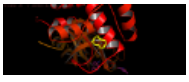
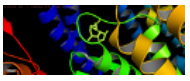
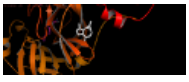
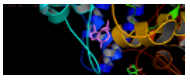
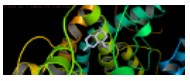
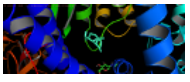
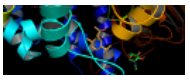
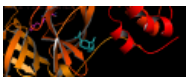
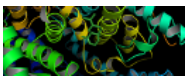
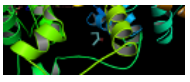
Table 1: Phytocomponents identified in the Ethanolic extract of Medicinal compound *AdathodaiKudineer*

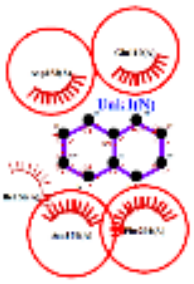
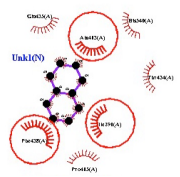
S.No	RT	Area %	Library/ID (C:\Database\NIST11.L)	Mol. F	Mol. W (g/mol)
1	5.259	1.86	Eucalyptol	$C_{10}H_{18}O$	154.25g/mol
2	5.259	1.86	Toluene	C_7H_8	92.14g/mol
3	10.200	11.06	2-Carene	$C_{10}H_{16}$	136.23g/mol
4	10.622	3.73	Alpha-Copaene	$C_{15}H_{24}$	204.35g/mol
5	10.777	7.84	1,6-Cyclodecadiene	$C_{10}H_{16}$	136.23g/mol
6	11.734	3.32	Aromadendrene	$C_{15}H_{24}$	204.35g/mol
7	11.907	1.89	Gamma-Murolene	$C_{15}H_{24}$	204.35g/mol
8	12.002	3.36	Beta-Copaene	$C_{15}H_{24}$	204.35g/mol
9	12.424	43.10	Cubebol	$C_{15}H_{26}O$	222.37g/mol
10	13.512	3.07	Selina-3,7 (11)-Diene	$C_{15}H_{24}$	204.35g/mol
11	25.898	3.65	2-Butanone	C_4H_8O	72.11g/mol

Molecular docking was performed between compounds identified in Siddha medicine *Adathodai Kudineer* with targets SARS-CoV-2 Virus main protease and Spike protein bound with ACE2 receptor, the results of the binding affinity of these compound with their respective targets are given in (Table 2).

Table 2: Binding affinity of the compounds with their respective targets

S.no	Compound name	PubChem ID	Binding energy for PDBID:6LU7 (KCal/mol)	Binding energyfor PDBID:6LZG (Kcal/mol)
1	Naphthalene	931	-5.5	-6.3
2	Benzene Propanol	31234	-5.0	-6.9
3	Benzene Acetic Acid	327550	-5.9	-6.9
4	Furazan-3-Amine	543119	-4.6	-5.2
5	Pyrazol-4-Carboxylic acid	643160	-4.5	-5.1
6	2(3H) Furanone	140765	-3.6	-4.1
7	Eucalyptol	2758	-5.1	-5.2
8	Toluene	1140	-4.2	-5.4
9	2-Carene	78249	-4.9	-6.3
10	Copaene	19725	-5.9	-6.5
11	Alpha-Copaene	70678558	-8.2	-10.9
12	1,6-Cyclodecadiene	5365639	-5.2	-5.6
13	Allomadendrene	42608158	-5.4	-6.5
14	Aromadendrene	91354	-6.5	-7.0
15	Gamma-Muurolene	12313020	-5.9	-8.0
16	Beta-Copaene	87529	-5.8	-6.6
17	Cubebol	11276107	-6.6	-7.4
18	Selina-3,7 (11)-Diene	522296	-6.1	-7.8
19	2-Butanone	6569	3.1	-3.8

S. no	Compound name	3D Docking pose of compounds with target 6LU7	3D Docking pose of compounds with target 6LZG
1	Naphthalene		
2	Benzene Propanol		
3	Benzene Acetic Acid		
4	Furazan-3-Amine		
5	Pyrazol-4-Carboxylic acid		
6	2(3H) Furanone		
7	Eucalyptol		
8	Toluene		
9	2-Carene		
10	Copaene		
11	Alpha-Copaene		
12	1,6-Cyclodecadiene		
13	Allomadendrene		
14	Aromadendrene		
15	Gamma-Muurolene		
16	Beta-Copaene		
17	Cubebol		
18	Selina-3,7 (11)-Diene		
19	2-Butanone		

S. no	Compound name	2D Plot of compounds with target 6LU7	2D Plot of compounds with target 6LZG
1	Naphthalene		
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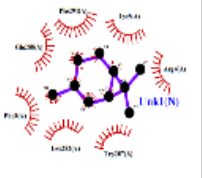
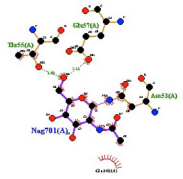
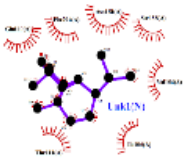
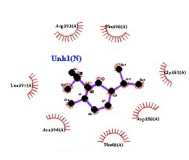
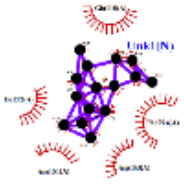
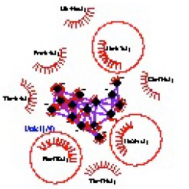
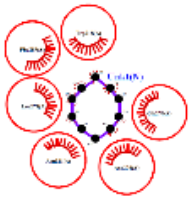
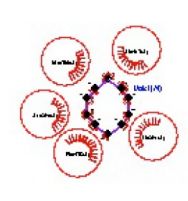
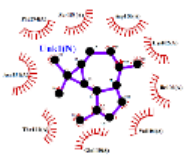
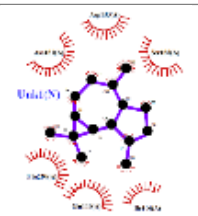
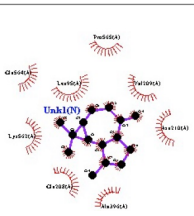
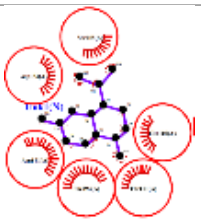
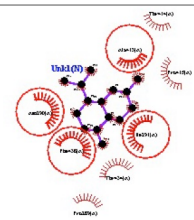
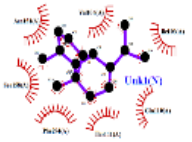
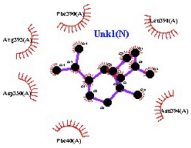
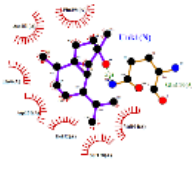
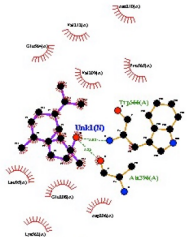
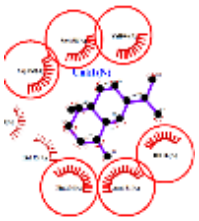
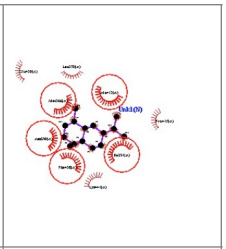
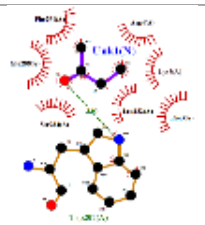
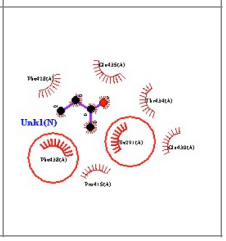
3	Benzene Acetic Acid		
4	Furazan-3-Amine		
5	Pyrazol-4-Carboxylic acid		
6	2(3H) Furanone		
7	Eucalyptol		
8	Toluene		

9	2-Carene		
10	Copaene		
11	Alpha-Copaene		
12	1,6-Cyclodecadiene		
13	Allomadendrene		
14	Aromadendrene		
15	Gamma-Murolene		
16	Beta-Copaene		
17	Cubedol		
18	Selina-3,7 (11)-Diene		
19	2-Butanone		

Discussion

ACE2 receptors are used by SARS-CoV-2 in the entry of the target cells to cause Corona Viral Disease 19 in Humans (2). The above mentioned compounds present in the aqueous and ethanolic extract of *Adathodai kudineer* Such as Napthalene, Benzene Propanol, Benzene Acetic Acid, Furazan-3-amine, Pyrazol-4-Carboxylic acid, 2(3H) Furanone, Eucalyptol, Toluene, 2-Carene, Alpha-Copaene, 1,6-Cyclodecadiene, Aromadendrene, Gamma-muurolene, Beta-copaene, Cubebol, Selina-3,7 (11) - Diene, 2-Butanonehaving minimum binding affinity against Spike protein (PDB ID 6LU7) and Spike protein ACE2 complex domain (PDB ID 6LZG) based on the molecular docking results. This indicates that there is a significant possibility of this molecules to inhibit the viral entry into target cellular pathway and replication. The exact mechanism behind this have to be studied further in various dimensions.

Molecular docking binding energy results and case report analysis on *Justicia adhatoda* L. leaves extract use for COVID 19 strongly recommended by researchers in prevention and treatment aspects (12)(13)(14). So, the therapeutic potency of this herbal present in AK will give a major impact for the treatment of SARS COV 2 infection. Research study confirms that the alcoholic extract of *Taxus baccata* has bronchodilator effect and can be able to decrease the bronchial hyper reactivity in experimental animals (15) The compound Glycyrrhizin present in the plant *Glycyrrhiza glabra L.* has antiviral effect. This plant has potent antiviral effect against Cytomegalo virus, SARS virus, Hepatitis A, B, C [16]. The Presence of Piperamides in the plant *Piper Longum L.* possess anti-viral against viruses related to upper respiratory tract infections and anti-proliferative effect (17).

Figure 3: ADME Alpha Copaene

Conclusion

The lead biomolecules which present in the Siddha drug *Adathodai Kudineer* such as Alpha-Copaene, Gamma-Muurolene, Selina-3,7 (11) – Diene, Cubebol, Aromadendrene have higher binding affinity towards theSARS-CoV-2 Spike Protein and ACE2 Receptor Spike protein Complex. Based on the findings of docking score values we can strongly suggest this Siddha poly herbal formulation *Adathodai kudineer* for the better management of COVID 19. Further preclinical and clinical trials have to be conducted in order to know the exact mechanism and efficacy of *Adathodai Kudineer* in SARS-CoV2 infection management.

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Appendix
ADME properties of all active compounds of *AdathodaiKudineer*

Table 3: Physiochemical properties of active compounds of *Adathodaikudineer* formulation predicted from SwissADME

Sl. No	Molecule	Formula	MW	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp3	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA
1	Naphthalene	C10H8	128.17	10	10	0	0	0	0	43.95	0
2	Benzene Propanol	C9H12O	136.19	10	6	0.33	3	1	1	42.18	20.23
3	Benzene Acetic Acid	C9H10BrNO2	244.09	13	6	0.22	3	3	2	53.53	63.32
4	Furazan-3-Amine	C2H2N4O3	130.06	9	5	0	1	5	1	27.52	110.76
5	Pyrazol-4-Carboxylic acid	C5H6N2O2	126.11	9	5	0.2	1	3	1	30.45	55.12
6	2(3H) Furanone	C4H4O2	84.07	6	0	0.25	0	2	0	20.04	26.3
7	Eucalyptol	C10H18O	154.25	11	0	1	0	1	0	47.12	9.23
8	Toluene	C7H8	92.14	7	6	0.14	0	0	0	31.41	0
9	2-Carene	C10H16	136.23	10	0	0.8	0	0	0	45.22	0
10	Copaene	C15H24	204.35	15	0	0.87	1	0	0	67.14	0
11	Alpha-Copaene	C15H24	204.35	15	0	0.87	1	0	0	67.14	0
12	1,6-Cyclodecadiene	C10H16	136.23	10	0	0.6	0	0	0	47.12	0
13	Allomadendrene	C15H24	204.35	15	0	0.87	0	0	0	67.14	0
14	Aromadendrene	C15H24	204.35	15	0	0.87	0	0	0	67.14	0
15	Gamma-Muurolene	C15H24	204.35	15	0	0.73	1	0	0	69.04	0
16	Beta-Copaene	C15H24	204.35	15	0	0.87	1	0	0	67.14	0
17	Cubedol	C15H26O	222.37	16	0	1	1	1	1	68.82	20.23

Table 4: Liphophilicity of active compounds of *Adathodaikudineer* formulation predicted from SwissADME

Sl.No	Molecule	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
1	Naphthalene	1.99	3.3	2.84	4.26	3.11	3.1
2	Benzene Propanol	1.95	1.88	1.61	2.19	2.35	2
3	Benzene Acetic Acid	1.34	-1.14	1.19	-0.66	1.55	0.46
4	Furazan-3-Amine	0.31	0.12	-0.43	-1.45	-1.42	-0.57
5	Pyrazol-4-Carboxylic acid	0.81	-0.24	0.12	-0.4	-0.26	0.01
6	2(3H) Furanone	1.19	0.22	0.45	-0.01	1.02	0.57
7	Eucalyptol	2.58	2.74	2.74	2.45	2.86	2.67
8	Toluene	1.85	2	2.73	3.52	2.44	2.51
9	2-Carene	2.66	3	2.85	4.29	2.79	3.12
10	Copaene	3.4	4.27	4.47	5.65	3.73	4.3
11	Alpha-Copaene	3.4	4.27	4.47	5.65	3.73	4.3
12	1,6-Cyclodecadiene	2.57	3.45	3.84	3.27	2.73	3.17
13	Allomadendrene	3.27	4.27	4.71	5.65	3.8	4.34
14	Aromadendrene	3.27	4.27	4.71	5.65	3.8	4.34
15	Gamma-Muurolene	3.38	4.58	4.31	4.63	4.01	4.18
16	Beta-Copaene	3.35	4.27	4.71	5.65	4.01	4.4
17	Cubedol	3.09	3.47	3.92	3.81	3.22	3.5

Table 5: Water solubility properties of all the active compounds of *AdathodaiKudineer* predicted from SWISS ADME

ESOL Log S	ESOL Solubility (mg/ml)	ESOL Solubility (mol/l)	ESOL Class	Ali Log S	Ali Solubility (mg/ml)	Ali Solubility (mol/l)	Ali Class	Silicos-IT LogSw	Silicos-IT Solubility (mg/ml)	Silicos-IT Solubility (mol/l)	Silicos-IT class
-3.45	4.51E-02	3.52E-04	Soluble	-2.98	1.36E-01	1.06E-03	Soluble	-4.03	1.19E-02	9.27E-05	Moderately soluble
-2.11	1.05E+00	7.68E-03	Soluble	-1.93	1.61E+00	1.18E-02	Very soluble	-3	1.35E-01	9.89E-04	Soluble
-0.78	4.06E+01	1.66E-01	Very soluble	0.3	4.89E+02	2.00E+00	Highly soluble	-2.72	4.61E-01	1.89E-03	Soluble
-1.07	1.11E+01	8.57E-02	Very soluble	-2	1.30E+00	9.96E-03	Soluble	0.15	1.83E+02	1.41E+00	Soluble
-0.82	1.93E+01	1.53E-01	Very soluble	-0.46	4.38E+01	3.47E-01	Very soluble	-0.13	9.37E+01	7.43E-01	Soluble
-0.5	2.66E+01	3.16E-01	Very soluble	-0.33	3.92E+01	4.66E-01	Very soluble	-0.04	7.67E+01	9.12E-01	Soluble
-2.52	4.63E-01	3.00E-03	Soluble	-2.59	3.98E-01	2.58E-03	Soluble	-2.45	5.45E-01	3.53E-03	Soluble

-2.77	1.58E-01	1.72E-03	Soluble	-2.38	3.80E-01	4.13E-03	Soluble	-2.69	1.88E-01	2.04E-03	Soluble
-2.48	4.51E-01	3.31E-03	Soluble	-2.51	4.22E-01	3.10E-03	Soluble	-2.23	8.06E-01	5.92E-03	Soluble
-3.86	2.84E-02	1.39E-04	Soluble	-4.19	1.32E-02	6.46E-05	Moderately soluble	-3.07	1.74E-01	8.51E-04	Soluble
-3.86	2.84E-02	1.39E-04	Soluble	-4.19	1.32E-02	6.46E-05	Moderately soluble	-3.07	1.74E-01	8.51E-04	Soluble
-3.1	1.07E-01	7.87E-04	Soluble	-3.54	3.97E-02	2.91E-04	Soluble	-1.7	2.75E+00	2.02E-02	Soluble
-4.07	1.72E-02	8.43E-05	Moderately soluble	-4.44	7.44E-03	3.64E-05	Moderately soluble	-3.32	9.83E-02	4.81E-04	Soluble
-4.07	1.72E-02	8.43E-05	Moderately soluble	-4.44	7.44E-03	3.64E-05	Moderately soluble	-3.32	9.83E-02	4.81E-04	Soluble
-3.76	3.58E-02	1.75E-04	Soluble	-4.02	1.94E-02	9.47E-05	Moderately soluble	-3.32	9.83E-02	4.81E-04	Soluble
-4.01	2.00E-02	9.81E-05	Moderately soluble	-4.44	7.44E-03	3.64E-05	Moderately soluble	-3.32	9.83E-02	4.81E-04	Soluble
-3.62	5.31E-02	2.39E-04	Soluble	-4.04	2.01E-02	9.04E-05	Moderately soluble	-2.73	4.10E-01	1.85E-03	Soluble
-3.9	2.55E-02	1.25E-04	Soluble	-4.16	1.42E-02	6.94E-05	Moderately soluble	-3.75	3.63E-02	1.78E-04	Soluble
-0.4	2.85E+01	3.95E-01	Very soluble	-0.21	4.44E+01	6.16E-01	Very soluble	-0.87	9.77E+00	1.36E-01	Soluble

Table 6: Pharmacokinetic properties of all the active compounds of *AdathodaiKudineer* predicted from SWISS ADME

GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
Low	Yes	No	Yes	No	No	No	No	-4.74
High	Yes	No	Yes	No	No	No	No	-5.8
High	Yes	No	No	No	No	No	No	-8.6
High	No	No	No	No	No	No	No	-7.01
High	No	No	No	No	No	No	No	-7.24
High	No	No	No	No	No	No	No	-6.66
High	Yes	No	No	No	No	No	No	-5.3
Low	No	No	Yes	No	No	No	No	-4.92
Low	Yes	No	No	No	No	No	No	-5.11
Low	Yes	No	Yes	Yes	Yes	No	No	-4.37
Low	Yes	No	Yes	Yes	Yes	No	No	-4.37
Low	Yes	No	No	No	No	No	No	-4.4
Low	Yes	No	Yes	Yes	Yes	No	No	-4.2
Low	Yes	No	Yes	Yes	Yes	No	No	-4.2
Low	No	No	No	Yes	Yes	No	No	-4.49
Low	Yes	No	Yes	Yes	Yes	No	No	-4.2
High	Yes	No	No	Yes	Yes	No	No	-4.87
Low	No	No	No	Yes	Yes	No	No	-4.39
High	Yes	No	No	No	No	No	No	-6.53

Table 7: Drug likeliness of all the active compounds of *AdathodaiKudineer* predicted from SWISS ADME

Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score
1	2	0	0	2	0.55
0	1	0	0	2	0.55
0	0	0	0	0	0.55
0	4	0	0	2	0.55
0	3	0	0	1	0.56
0	3	0	0	2	0.55
0	1	0	0	2	0.55
0	3	0	0	2	0.55
1	1	0	0	2	0.55
1	0	0	0	1	0.55
1	0	0	0	1	0.55
0	1	0	0	2	0.55
1	0	0	0	1	0.55
1	0	0	0	1	0.55
1	0	0	0	1	0.55

1	0	0	0	1	0.55
0	0	0	0	1	0.55
1	0	0	0	1	0.55
0	3	0	0	3	0.55

Table 8: Medicinal chemistry properties of all the active compounds of *AdathodaiKudineer* predicted from SWISS ADME

PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
0	0	1	1
0	0	1	1
0	1	1	2.04
0	2	1	2.8
0	0	1	1.09
0	0	1	2.33
0	0	1	3.65
0	0	1	1
0	1	1	3.84
0	1	2	4.62
0	1	2	4.62
0	1	2	2.99
0	1	2	3.7
0	1	2	3.7
0	1	2	4.35
0	1	2	3.91
0	0	2	4.13
0	1	2	4.14
0	0	1	1

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