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Original Research Article

Pharmacokinetics and Molecular Docking Study of Siddha Polyherbal Preparation Shailam Against COVID-19 Mutated s Gene

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ABSTRACT

COVID-19 is a deadly disease; at the time of the first COVID-19 wave (January 2020 to November 2020), so many deaths were reported worldwide. There were no standard conventional treatments and vaccines, so the whole world turned to traditional medicine. Siddha system of medicine is one of the traditional medicines practiced in the southern part of India. *Shailam* is a polyherbal formulation (licence no. 1189/25D) which was analyzed by molecular docking, with AutoDockVina software, against SARS-CoV-2 Spike Protein (PDB ID 7DDD). Absorption, distribution, metabolism, and excretion (ADME) properties were also recorded for *Shailam's* phytocompounds using the online SwissADME tool. The results of the molecular docking study showed that the phytocompounds, like Caryophyllene, Aspidospermidin-17-ol, N,N'Dibenzylidene-3,3'-dichlorobenzidine, Beta-selinene, Curzerene, Germacrene B, Spathulenol, had the highest docking scores: -6.6 Kcal/mol, -8.8 Kcal/mol, -8.7 Kcal/mol, -6.2 Kcal/mol, -6.0 Kcal/mol, -6.6 Kcal/mol, -6.5 Kcal/mol, respectively, and the scores fall within the docking score range of the four standard conventional drugs; Azithromycin, Hydroxychloroquinone, Ivermectin, and Remdesivir which had binding energies of 7.7 Kcal/mol, -5.9 Kcal/mol, -9.2 Kcal/mol, and -7.5 Kcal/mol, respectively. ADME analysis predicted that all of *Shailam's* phytocompounds met four Lipinski's rule of five and have a higher bioavailability score (0.55) as compared to standard conventional drugs, Azithromycin, Hydroxychloroquinone, Ivermectin, and Remdesivir (0.17). Twelve of *Shailam's* phytochemical compounds have high GIT absorption and can cross the blood–brain barrier (BBB). In conclusion, Shailam's phytocompounds show a good docking score and ADME property against SARS-CoV-2 Spike Protein (PDB ID 7DDD**)** as compared to standard conventional drugs.

Keywords: Siddha medicine, COVID-19, Herbal medicine, Alternative medicine, Traditional medicine.

Introduction

The human community has faced many pandemics in the past, in which COVID-19 is a deadly disease that originated in December 2019 in Wuhan, China. The World Health Organization (WHO) later declared COVID-19 as a pandemic in February 2020 and named it coronavirus disease-2019 (COVID-19).[1] The COVID-19 virus is the seventh coronavirus to infect humans; it is the third in recent years causing widespread infectious disease, leading to more severe respiratory infections and deaths worldwide. As of March 17, 2022, the outbreak of COVID-19 was in over 210 countries and territories and has infected about 450 million people, with six million people dying as a result. The most affected countries include the USA (17.95%), India (15.71%), and Brazil (9.91%).[2]

The world suffered drastic damage in terms of both human health and economy. Although vaccination started in January 2021, only 56.6% of the world population was completely vaccinated and 68.3% received the first vaccine dose.[3]

WHO Director-General Dr. Tedros Adhanom Ghebreyesus said that the pandemic could end in mid-2022 when vaccination is complete for 70% of the population, until traditional medicine could be the only hope for this pandemic.[4] The Siddha medicine is a type of traditional medicine used in the southern India. Siddhars are spiritual scientists who practiced this knowledge and passed it on to humanity.

Siddha medicine system has different forms of medicine; 32 internal and 32 external, Shailam is a Siddha polyherbal formulation having 20 ingredients.[5](Table 1), which has already proven its efficacy in clinical trials, and most of the Siddha medicines have been used in practice for so many years. Usually, traditional medicines like Chinese traditional medicine, Ayurveda, and Unani were practiced widely among the people of a certain region and they have been tested pharmacologically. Therefore, this study was conducted to demonstrate *In silico* efficacy of Shailam, a Siddha polyherbal formulation against SARS-CoV-2 Spike Protein (PDB ID 7DDD) and to study SwissADME property of *Shailam's* phytocompounds.

Materials and Methods

Molecular docking

The "key-and-lock" theory is used in molecular docking to discover the appropriate orientation of protein and ligand. **PDB ID 7DDD** target protein was docked with the selected phytochemical compounds using the AutoDock Vina software, and the binding energies were calculated. The ligands and target protein were synthesized, following routine ligand and protein preparation procedures, and the protein and ligand files were then uploaded to AutoDock Vina.[28]

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Table 1: Siddha preparation, *Shailam* Ingredients, Phytocompounds and its Pharmacological activity

Sl.no	Compound name	Formula	Molecular Weight	Botanical name	Pharmacological Activity
1	Eugenol	$C_{10}H_{12}O_2$	164.2	*Ocimum tenuiflorum*	*Antiaflatoxigenic, Genotoxicity, Antifungal*[6-8]
2	Caryophyllene	$C_{15}H_{24}$	204.35	*Ocimum tenuiflorum*	*Antibacterial, Anti-inflammatory, Anticonvulsant*[9-11]
3	Amrinone	$C_{10}H_9N_3$	187.2	*Justicia adhatoda*	*Muscle inhibition Cardiotonic*[12,13]
4	Phytol	$C_{20}H_{40}O$	296.53	*Justicia adhatoda*	*Hepatoprotective*[14,15]
5	2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	$C_{11}H_{14}O_2$	178.23	*Glycyrrhiza glabra*	
6	1,5-Hexadiyne	C_6H_6	78.11	*Glycyrrhiza glabra*	
7	Isopinocarveol	$C_{10}H_{16}O$	152.23	*Tinospora cordifolia*	
8	Di-n-Decylsulfone	$C_{20}H_{42}O_2$	346.61	*Tinospora cordifolia*	
9	1,8-cineole	$C_{10}H_{18}O$	154.25	*Elettaria cardamomum*	*Mucolytic, Anti-inflammatory, Antitumor*[16,17]
10	Aspidospermidin-17-ol	$C_{23}H_{30}N_2$	414.49	*Solanum virginianum*	
11	N,N'Dibenzylidene-3,3'-dichlorobenzidine	$C_{26}H_{18}Cl$	429.34	*Solanum virginianum*	
12	Linolenic acid	$C_{18}H_{30}O_2$	278.43	*Azadirachta indica*	*Anti-inflammatory, Antitumor, Antibacterial*[18–20]
13	Hexadecanoic acid	$C_{16}H_{32}O_2$	256.42	*Trigonella foenum-graecum*	*Bactericidal* [21]
14	Terpinen-4-ol	$C_{10}H_{18}O$	154.25	*Myristica fragrans*	*Acaricidal, Anticonvulsant, Antibacterial*[22-24]
15	Sabinene	$C_{10}H_{16}$	136.23	*Myristica fragrans*	
16	Beta-selinene	$C_{15}H_{24}$	204.35	*Commiphora myrrh*	
17	Curzerene	$C_{15}H_{20}O$	216.32	*Commiphora myrrh*	*Antileishmanial activity*[25]
18	Germacrene B	$C_{15}H_{24}$	204.35	*Commiphora myrrh*	
19	Myrcenol	$C_{10}H_{18}O$	154.25	*Commiphora myrrh*	
20	Spathulenol	$C_{15}H_{24}O$	220.35	*Commiphora myrrh*	*Anti-mycobacterial, Immunomodulatory*[26,27]

For the current work, 20 phytochemical compounds or bioactive compounds identified from *Shailam* were used for the docking study. The chemical structures of all selected compounds were retrieved from the *National Center for Biotechnology Information* (NCBI's) PubChem compound database.[29]

Swiss ADME

To estimate individual absorption, distribution, metabolism, and excretion (ADME) characteristics of *Shailam's* phytocompounds, the SwissADME software of the Swiss Institute of Bioinformatics, a web server displaying the SwissADME Submission page, was accessed from Google.[30] The list is designed to contain one input molecule per row with multiple inputs, such as defined by the simplified molecular-input line-entry system (SMILES), with the results presented in graphs, tables, and an Excel spreadsheet for each molecule.

Results and Discussion

Molecular docking

The biological activity of *Shailam* compounds against SARS-CoV-2 Spike Protein (PDB ID 7DDD) was evaluated using the 3D

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composition of the receptor retrieved from the protein data library site of SARS-CoV-2 Spike Protein (PDB ID 7DDD**).** Various compounds from *Shailam* were interacted with the SARS-CoV-2 Spike Protein (PDB ID 7DDD) as shown in Figure 1. The docking results of *Shailam* bioactive molecules and standard drugs are shown in Table 2. Docking studies show that the ligands bind to the active spot region of SARS-CoV-2 Spike Protein (PDB ID 7DDD**)** with good binding energy as compared to the standard control drugs, presented in the form of e-negative values. Higher negative e-values in docking scores indicate strong binding affinity between the receptor and ligand molecules, indicating that the bioactive substances are more efficient. Thus, it is clear that the bioactive compounds were able to effectively interact with all available binding sites of the SARS-CoV-2 Spike Protein (PDB ID 7DDD**)**.

Shailam's compounds show docking score ranging from 3.8 to 8.8. The compounds like Caryophyllene, Aspidospermidin-17-ol, N,N'Dibenzylidene-3,3'-dichlorobenzidine, Beta-selinene, Curzerene, Germacrene B, Spathulenol showed the highest docking scores -6.6 Kcal/mol, -8.8 Kcal/mol, -8.7 Kcal/mol, -6.2 Kcal/mol, -6.0 Kcal/mol, -6.6 Kcal/mol, -6.5 Kcal/mol, respectively, among the 20 phytochemical compounds, and the scores fall within the docking score range of the four standard conventional drugs Azithromycin, Hydroxychloroquinone, Ivermectin, Remdesivir which have binding energies of 7.7 Kcal/mol, -5.9 Kcal/mol, -9.2 Kcal/mol, -7.5 Kcal/mol, respectively.

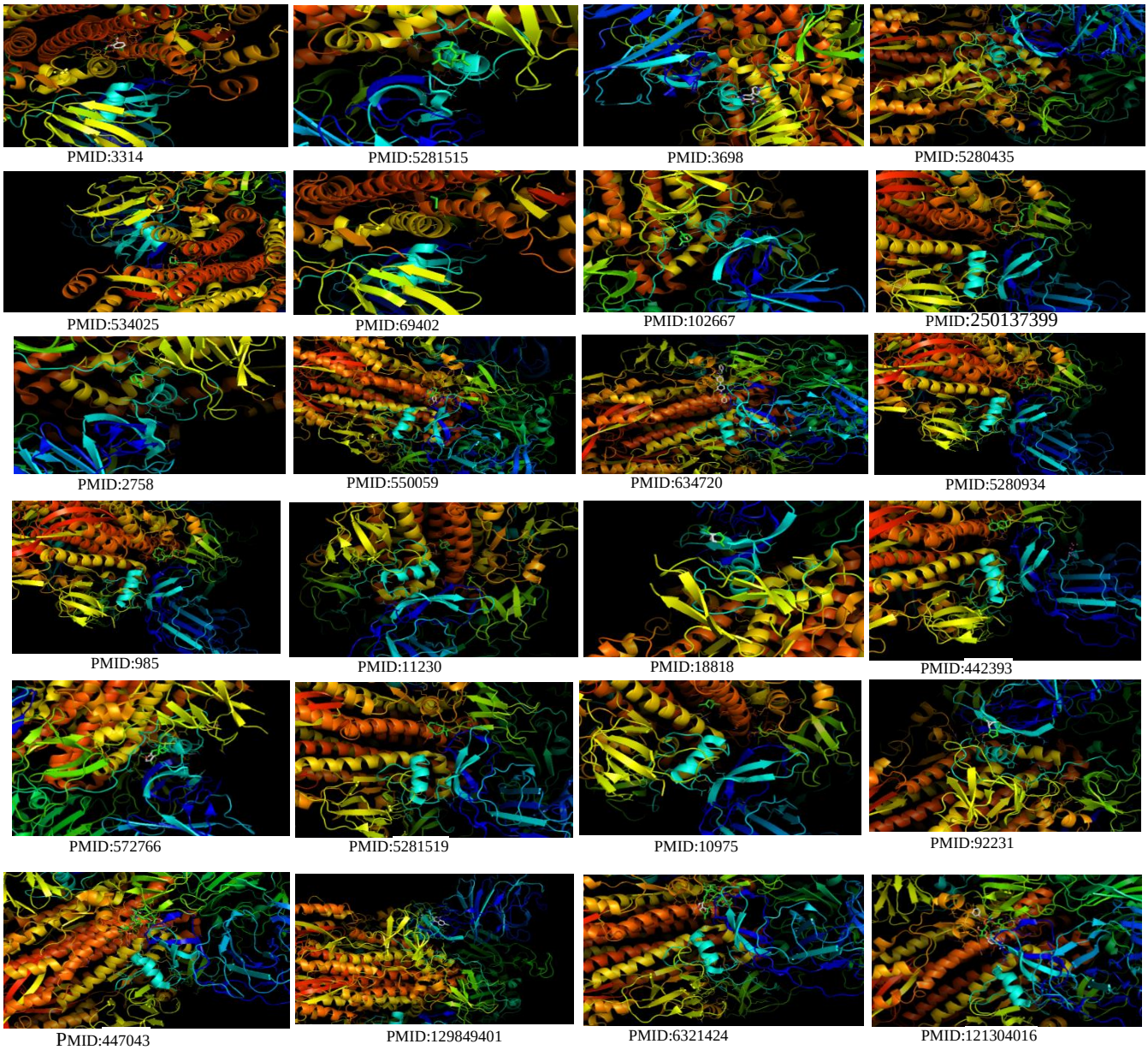

Figure 1: Molecular docking of target SARS-CoV-2 Spike Protein (PDB ID 7DDD) by phytocompounds of Shailam, Eugenol, Caryophyllene, Amrinone, Phytol, 2-(2,5 Hexadiynyloxy)tetrahydro-2H-pyran, 1,5-Hexadiyne, Isopinocarveol, Di-n-Decylsulfone, 1,8-cineole, Aspidospermidin-17-ol, N,N'Dibenzylidene-3,3'-dichlorobenzidine, Linolenic acid, Hexadecanoic acid, Terpinen-4-ol, Sabinene, Beta-selinene, Curzerene, Germacrene B, Myrcenol, Spathulenol, Azithromycin, Hydroxychloroquinone, Ivermectin, Remdesivir

SwissADME

The rationale for these *In silco* techniques came from the fact that they cost less and take less time than regular ADME profiling. For example, in an *in silico* model, analyzing 20,000 compounds takes a fraction of a second, whereas in a "wet" laboratory, the same process takes 20 weeks. Many pharmaceutical companies are increasingly

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adopting computer models to replace "wet" screens, owing to ADME data that was pooled in the late 1990s. Various theoretical models for estimating ADME parameters were created on the basis of this paradigm shift. Quantitative structure–activity relationships, QSAR, and knowledge-base approaches are frequently utilized in software tools intended to predict the ADME features of potential drug candidates.[31] The present study used SwissADME online software tool which is available free for the users to evaluate the ADME properties.

The drug-likeness of active ingredients has been studied to determine if they have good ADME properties. The aqueous solubility of drug-like molecules should be good as estimated by three techniques: ESOL, (ALI) logS, and (SILICOS-IT) logS. Orally bioavailable drugs must follow Lipinski's rule of five in Table 3, which require a molecular weight (MW) of not more than 500 g/mol, H-bond acceptors of not more than 10, H-bond donors of not more than 5, logP value of not more than 5, and number of rotatable bonds not less than 10, where a violation of two or more rules indicates that the molecule is orally inactive.

Drug-likeness analyses of phytocompounds are tabulated in Table 4. The phytocompounds, such as Eugenol, Amrinone, 2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran, 1,5-Hexadiyne, Isopinocarveol, 1,8-cineole, Aspidospermidin-17-ol, Terpinen-4-ol, Curzerene, Myrcenol, Spathulenol, followed all Lipinski's rule of five, and only some *Shailam's* compounds like Caryophyllene, Phytol, Di-n-Decylsulfone, N,N'Dibenzylidene-3,3'-dichlorobenzidine, Linolenic acid, Hexadecanoic acid, Sabinene, Beta-selinene, Germacrene B which violate one Lipinski's rule have rotatable bonds less than 10, while standard drugs Azithromycin, Ivermectin, Remdesivir violate 2 Lipinski's rules such as molecular weight, H-bond acceptor over 10, H-bond donor under 5.

Table 2: *Shailam* compounds and docking score

S/l no	Compound name	Docking score with target protein PDB ID 7DDD
1	Eugenol	-5.4 Kcal/mol
2	Caryophyllene	-6.6 Kcal/mol
3	Amrinone	-5.7 Kcal/mol
4	Phytol	-4.5 Kcal/mol
5	2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	-5.0 Kcal/mol
6	1,5-Hexadiyne	-3.8 Kcal/mol
7	Isopinocarveol	-5.3 Kcal/mol
8	Di-n-Decylsulfone	-4.9 Kcal/mol
9	1,8-cineole	-5.2 Kcal/mol
10	Aspidospermidin-17-ol	-8.8 Kcal/mol
11	N,N'Dibenzylidene-3,3'-dichlorobenzidine	-8.7 Kcal/mol
12	Linolenic acid	-5.2 Kcal/mol
13	Hexadecanoic acid	-4.6 Kcal/mol
14	Terpinen-4-ol	-5.1 Kcal/mol
15	Sabinene	-5.0 Kcal/mol
16	Beta-selinene	-6.2 Kcal/mol
17	Curzerene	-6.0 Kcal/mol
18	Germacrene B	-6.6 Kcal/mol
19	Myrcenol	-4.6 Kcal/mol
20	Spathulenol	-6.5 Kcal/mol
21	Azithromycin	-7.7 Kcal/mol
22	Hydroxychloroquinone	-5.9 Kcal/mol
23	Ivermectin	-9.2 Kcal/mol
24	Remdesivir	-7.5 Kcal/mol

Compounds with a logP higher above 1 and less below 4 are often more likely to get better physicochemical as well as ADME qualities for oral medications.[32] Among the four standard drugs, Remdesivir alone has good lipophilicity (Table 5). All phytocompounds, other than Phytol, Di-n-Decylsulfone,N,N'Dibenzylidene-3,3'-dichlorobenzidine, Linolenic acid, have good ADME properties for oral drugs. Furthermore, for oral administration discovery studies, solubility is one of the most important factors determining absorption. A medicine intended for parenteral administration must also be highly water soluble so as to deliver a sufficient amount of active component in the small volume of such pharmaceutical dosage. SwissADME includes two topological approaches to predict water solubility. The first one is based on the ESOL model while the second is based on Ali *et al*.[33] Di-n-Decylsulfone1,8-cineole, N,N'Dibenzylidene-3,3'-dichlorobenzidine, and only these two compounds of *Shailam* are slightly aqueous soluble, while all other eighteen compounds have good solubility (Table 6).

Table 3: Lipinski's rule of five (Ro5) violation

Rules	Values
Molecular weight	< 500 Daltons
Hydrogen bond acceptors No	> 10
Number of rotatable bonds No	< 10
Hydrogen bond donors No	> 5
Octanol–water partition coefficient (logP)	< 5

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Table 4: General Characteristics of Phytoconstituents of *Shailam*

Molecule	Canonical SMILES	Formula	MW	Heavy atoms	Aromatic heavy atoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
Eugenol	COC1=C(C=CC(=C1)CC=C)O	$C_{10}H_{12}O_2$	164.2	12	6	0.2	3	2	1	49.06	29.46
Caryophyllene	CC1=CCCC(=C)C2CC(C2CC1)(C)C	$C_{15}H_{24}$	204.35	15	0	0.73	0	0	0	68.78	0
Amrinone	C1=CN=CC=C1C2=CNC(=O)C(=C2)N	$C_{10}H_9N_3$	187.2	14	12	0	1	2	2	54.7	71.77
Phytol	CC(C)CCCC(C)CCCC(C)CCCC(=CCO)C	$C_{20}H_{40}O$	296.53	21	0	0.9	13	1	1	98.94	20.23
2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	C#CCC#CCOC1CCCCO1	$C_{11}H_{14}O_2$	178.23	13	0	0.64	2	2	0	51.37	18.46
1,5-Hexadiyne	C#CCCC#C	C_6H_6	78.11	6	0	0.33	1	0	0	27.28	0
Isopinocarveol	CC1(C2CC1C(=C)C(C2)O)C	$C_{10}H_{16}O$	152.23	11	0	0.8	0	1	1	46.38	20.23
Di-n-Decylsulfone	CCCCCCCCCCS(=O)(=O)CCCCCCCCCC	$C_{20}H_{42}O_2$	346.61	23	0	1	18	2	0	107.22	42.52
1,8-cineole	CC1(C2CCC(O1)(CC2)C)C	$C_{10}H_{18}O$	154.25	11	0	1	0	1	0	47.12	9.23
Aspidospermidin-17-ol	CC(=O)N1C2CCC34CCCN5C3(C2(CC5)C6=CC(=C(C(=C61)O)OC)OC)OCC4	$C_{23}H_{30}N_2$	414.49	30	6	0.7	3	6	1	118.43	71.47
N,N'Dibenzylidene-3,3'-dichlorobenzidine	C1=CC=C(C=C1)C=NC2=C(C=C(C=C2)C3=CC(=C(C=C3)N=CC4=CC=CC=C4)Cl)Cl	$C_{26}H_{18}Cl$	429.34	30	24	0	5	2	0	129.29	24.72

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Linolenic acid	CCC=CCC=CCC=CCCCCCCCC(=O)O	$C_{18}H_{30}O_2$	278.43	20	0	0.61	13	2	1	88.99	37.3
Hexadecanoic acid	CCCCCCCCCCCCCCCC(=O)O	$C_{16}H_{32}O_2$	256.42	18	0	0.94	14	2	1	80.8	37.3
Terpinen-4-ol	CC1=CCC(CC1)(C(C)C)O	$C_{10}H_{18}O$	154.25	11	0	0.8	1	1	1	48.8	20.23
Sabinene	CC(C)C12CCC(=C)C1C2	$C_{10}H_{16}$	136.23	10	0	0.8	1	0	0	45.22	0
Beta-selinene	CC(=C)C1CCC2(CCCC(=C)C2C1)C	$C_{15}H_{24}$	204.35	15	0	0.73	1	0	0	68.78	0
Curzerene	CC1=COC2=C1CC(C(C2)(C)C=C)C(=C)C	$C_{15}H_{20}O$	216.32	16	5	0.47	2	1	0	68.74	13.14
Germacrene B	CC1=CCCC(=CCC(=C(C)C)CC1)C	$C_{15}H_{24}$	204.35	15	0	0.6	0	0	0	70.68	0
Myrcenol	CC(C)(CCCC(=C)C=C)O	$C_{10}H_{18}O$	154.25	11	0	0.6	5	1	1	50.44	20.23
Spathulenol	CC1(C2C1C3C(CCC3(C)O)C(=C)CC2)C	$C_{15}H_{24}O$	220.35	16	0	0.87	0	1	1	68.34	20.23
Azithromycin	CCC1C(C(C(N(CC(CC(C(C(C(C(=O)O1)C)OC2CC(C(C(O2)C)O)(C)OC)C)OC3C(C(CC(O3)C)N(C)C)O)(C)O)C)C)O)(C)O	$C_{38}H_{72}N_2$	748.98	52	0	0.97	7	14	5	200.78	180.08
Hydroxychloroquinone	C1(=C(C(=O)C2=C(C1=O)OS(=O)(=O)O2)Cl)O	C_6HClO_7S	252.59	15	0	0	0	7	1	43.68	115.35
Ivermectin	CCC(C)C1C(CCC2(O1)CC3CC(O2)CC=C(C(C(C=CC=C4COC5C4(C(C=C(	$C_{48}H_{74}O1$	875.09	62	0	0.81	8	14	3	230.77	170.06

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	C5O)C)C(=O)O3)O)C)OC6CC(C(C(O6)C)OC7CC(C(C(O7)C)O)OC)OC)C)C										
Remdesivir	COC1=C(C=CC(=C1)CC=C)O	$C_{27}H_{35}N_6$	602.58	42	15	0.48	14	12	4	150.43	213.36

Table 5: Lipophilicity of active compounds of *Shailam* formulation predicted from SwissADME

Molecule	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
Eugenol	2.37	2.27	2.13	2.01	2.48	2.25
Caryophyllene	3.29	4.38	4.73	4.63	4.19	4.24
Amrinone	1.14	-0.16	1.03	0.18	1.88	0.81
Phytol	0	8.19	6.36	5.25	6.57	5.28
2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	2.85	1.74	1.72	1.97	2.56	2.17
1,5-Hexadiyne	2.05	1.38	1.19	3.26	1.44	1.86
Isopinocarveol	2.12	1.79	1.97	2.3	2.15	2.07
Di-n-Decylsulfone	5.05	8.6	7.76	5.03	6.95	6.68
1,8-cineole	2.58	2.74	2.74	2.45	2.86	2.67
Aspidospermidin-17-ol	3.39	2	2.02	2	2.44	2.37
N,N'Dibenzylidene-3,3'-dichlorobenzidine	4.28	7.4	8.16	6.02	8.67	6.91
Linolenic acid	0	6.46	5.66	4.38	5.59	4.42
Hexadecanoic acid	3.85	7.17	5.55	4.19	5.25	5.2
Terpinen-4-ol	2.51	3.26	2.5	2.3	2.44	2.6
Sabinene	2.65	3.09	3	4.29	3.23	3.25
Beta-selinene	3.28	5.44	4.73	4.63	4.43	4.5
Curzerene	3.17	4.65	4.07	3.33	4.69	3.98
Germacrene B	3.27	5.77	5.18	4.53	4.25	4.6
Myrcenol	2.65	3.01	2.67	2.59	2.52	2.69
Spathulenol	2.88	3.11	3.39	3.67	3.27	3.26
Azithromycin	4.76	4.02	1.52	-0.44	0.24	2.02
Hydroxychloroquinone	0.39	0.62	0.73	-2.18	-0.1	-0.11
Ivermectin	0	6.34	5.6	1.25	2.72	3.18
Remdesivir	3.24	1.91	2.21	0.18	-0.05	1.5

The importance of gastrointestinal (GI) absorption in maintaining appropriate therapeutic levels in the systemic circulation cannot be overemphasized. Drugs or potential compounds must be absorbed through the gastrointestinal tract and enter the systemic circulation in sufficient amounts or quantities to reach their target.[34] Drugs that are highly absorbed from the GI tract easily reach their target site and have a therapeutic effect. Out of four conventional drugs, Hydroxychloroquinone has high GIT absorption, and twelve *Shailam's* phytocompounds like Eugenol, Amrinone, 2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran, Isopinocarveol, 1,8-cineole, Aspidospermidin-17-ol, Linolenic acid, Hexadecanoic acid, Terpinen-4-ol, Curzerene, Myrcenol, Spathulenol have high GIT absorption (Table7).

Twelve *Shailam's* phytocompounds such as Eugenol, Caryophyllene, Amrinone, Phytol, Di-n-Decylsulfone, Aspidospermidin-17-ol, N,N'Dibenzylidene-3,3'-dichlorobenzidine, Hexadecanoic acid, Beta-selinene, Curzerene, Germacrene B, Spathulenol are inhibitors of CYP1A2, CYP2C19 CYP2C9, CYP2D6 CYP3A4, enzyme (Table7). Inhibition of CYP3A4 has previously been found to reduce the probability of drug clearance from the systemic circulation and improve drug bioavailability.

The blood–brain barrier (BBB) is a protective system developed by the endothelial cells lining cerebral microvessels. The drugs or compounds that are not soluble in lipids with a molecular weight greater than 400 Dalton cannot penetrate the BBB, but smaller, lipophilic molecules can go across the BBB.[35] Accordingly, when

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formulating a medicine for neurodegenerative and associated disorders, the BBB permeability parameter is always taken into account. None of the four standard conventional drugs was predicted to permeate the BBB, and twelve phytocompounds from Shailam were predicted to go across the BBB, namely Eugenol, 2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran, Isopinocarveol, 1,8-cineole, Aspidospermidin-17-ol, Linolenic acid, Hexadecanoic acid, Terpinen-4-ol, Sabinene, Curzerene, Myrcenol, Spathulenol (Table7).

The degree of absorption and fraction of a given amount of unaltered medicine that enters the circulatory system are measured by drug bioavailability. When estimating pharmacological dosages, this is a crucial pharmacokinetic aspect of the medicine that should be thoroughly investigated. A higher level of bioavailability is required for a drug to reach a higher and optimal concentration in the circulatory system and exert a pharmacological effect. All of Shailam's phytochemical compounds have a higher bioavailability score (0.55) as compared to standard conventional drugs, Azithromycin, Hydroxychloroquinone, Ivermectin, Remdesivir (0.17). *Shailam* compounds such as Linolenic acid and Hexadecanoic acid (0.85) also have a higher bioavailability as standard drug Hydroxychloroquinone (0.56) (Table8).

Synthetic accessibility (SA) is an important factor to consider in drug selection. Certainly, medicinal chemists are best at determining SA for a reasonable number of compounds. When there are too many molecular structures to evaluate manually, *in silico* estimation can be used as a pre-filter. Ertl and Schuffenhauer offered a fingerprint-based SA estimation solution, but it included closed-source fingerprint-defining information, which made it difficult to use in practice. The SA score ranges from 1 (very easy) to 10 (very difficult) (Table 9). Here, all phytocompounds have SA score below 5, which means they are easily converted into a synthetic form.

Table 6: Water solubility properties of all the active compounds of *Shailam* predicted from SwissADME

Molecule	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
Eugenol	-2.46	5.69E-01	3.47E-03	Soluble	-2.53	4.90E-01	2.98E-03	Soluble	-2.79	2.65E-01	1.61E-03	Soluble
Caryophyllene	-3.87	2.78E-02	1.36E-04	Soluble	-4.1	1.64E-02	8.01E-05	Moderately soluble	-3.77	3.49E-02	1.71E-04	Soluble
Amrinone	-1.47	6.37E+00	3.40E-02	Very soluble	-0.89	2.40E+01	1.28E-01	Very soluble	-3.72	3.58E-02	1.91E-04	Soluble
Phytol	-5.98	3.10E-04	1.05E-06	Moderately soluble	-8.47	9.94E-07	3.35E-09	Poorly soluble	-5.51	9.06E-04	3.05E-06	Moderately soluble
2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	-1.91	2.20E+00	1.23E-02	Very soluble	-1.74	3.21E+00	1.80E-02	Very soluble	-1.49	5.74E+00	3.22E-02	Soluble
1,5-Hexadiyne	-1.13	5.82E+00	7.45E-02	Very soluble	-0.98	8.12E+00	1.04E-01	Very soluble	-0.73	1.45E+01	1.86E-01	Soluble
Isopinocarveol	-1.91	1.87E+00	1.23E-02	Very soluble	-1.83	2.23E+00	1.47E-02	Very soluble	-1.69	3.14E+00	2.07E-02	Soluble
Di-n-Decylsulfone	-6.22	2.09E-04	6.04E-07	Poorly soluble	-9.37	1.48E-07	4.28E-10	Poorly soluble	-7.83	5.15E-06	1.49E-08	Poorly soluble
1,8-cineole	-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
Aspidospermidin-17-ol	-3.62	9.95E-02	2.40E-04	Soluble	-3.13	3.09E-01	7.46E-04	Soluble	-4.06	3.58E-02	8.63E-05	Moderately soluble
N,N'Dibenzylidene-3,3'-dichlorobenzidine	-7.43	1.61E-05	3.75E-08	Poorly soluble	-7.75	7.65E-06	1.78E-08	Poorly soluble	-11.26	2.35E-09	5.47E-12	Insoluble
Linolenic acid	-4.78	4.64E-03	1.67E-05	Moderately soluble	-7.04	2.55E-05	9.16E-08	Poorly soluble	-3.96	3.08E-02	1.11E-04	Soluble

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Hexadecanoic acid	-5.02	2.43E-03	9.49E-06	Moderately soluble	-7.77	4.31E-06	1.68E-08	Poorly soluble	-5.31	1.25E-03	4.88E-06	Moderately soluble
Terpinen-4-ol	-2.78	2.54E-01	1.64E-03	Soluble	-3.36	6.75E-02	4.38E-04	Soluble	-1.91	1.92E+00	1.24E-02	Soluble
Sabinene	-2.57	3.71E-01	2.72E-03	Soluble	-2.76	2.38E-01	1.75E-03	Soluble	-2.48	4.55E-01	3.34E-03	Soluble
Beta-selinene	-4.47	6.95E-03	3.40E-05	Moderately soluble	-5.2	1.30E-03	6.36E-06	Moderately soluble	-3.8	3.27E-02	1.60E-04	Soluble
Curzerene	-4.21	1.33E-02	6.17E-05	Moderately soluble	-4.65	4.82E-03	2.23E-05	Moderately soluble	-4.54	6.25E-03	2.89E-05	Moderately soluble
Germacrene B	-4.74	3.70E-03	1.81E-05	Moderately soluble	-5.54	5.91E-04	2.89E-06	Moderately soluble	-3.75	3.63E-02	1.78E-04	Soluble
Myrcenol	-2.36	6.69E-01	4.34E-03	Soluble	-3.1	1.23E-01	7.95E-04	Soluble	-2.22	9.32E-01	6.04E-03	Soluble
Spathulenol	-3.17	1.51E-01	6.83E-04	Soluble	-3.2	1.38E-01	6.26E-04	Soluble	-2.96	2.39E-01	1.09E-03	Soluble
Azithromycin	-6.55	2.09E-04	2.79E-07	Poorly soluble	-7.5	2.34E-05	3.13E-08	Poorly soluble	-2.22	4.48E+00	5.98E-03	Soluble
Hydroxychloroquinone	-1.8	4.03E+00	1.60E-02	Very soluble	-2.62	6.10E-01	2.42E-03	Soluble	-0.71	4.91E+01	1.95E-01	Soluble
Ivermectin	-8.73	1.62E-06	1.85E-09	Poorly soluble	-9.7	1.74E-07	1.99E-10	Poorly soluble	-3.89	1.13E-01	1.29E-04	Soluble
Remdesivir	-4.12	4.58E-02	7.59E-05	Moderately soluble	-6.01	5.84E-04	9.69E-07	Poorly soluble	-4.77	1.03E-02	1.71E-05	Moderately soluble

Table 7: Pharmacokinetic Parameters of the Phytoconstituents of *Shailam* predicted from SwissADME

Molecule	**GI absorption**	**BBB permeability**	**Pgp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**	**log Kp (cm/s)**
Eugenol	High	Yes	No	Yes	No	No	No	No	-5.69
Caryophyllene	Low	No	No	No	Yes	Yes	No	No	-4.44
Amrinone	High	No	No	Yes	No	No	No	No	-7.56
Phytol	Low	No	Yes	No	No	Yes	No	No	-2.29
2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	High	Yes	No	No	No	No	No	No	-6.15
1,5-Hexadiyne	Low	No	No	No	No	No	No	No	-5.8
Isopinocarveol	High	Yes	No	No	No	No	No	No	-5.96
Di-n-Decylsulfone	Low	No	No	Yes	No	Yes	No	No	-2.31
1,8-cineole	High	Yes	No	No	No	No	No	No	-5.3
Aspidospermidin-17-ol	High	Yes	No	No	Yes	No	Yes	No	-7.41
N,N'Dibenzylidene-3,3'-dichlorobenzidine	Low	No	Yes	Yes	No	No	No	Yes	-3.66
Linolenic acid	High	Yes	Yes	No	No	No	No	No	-3.41

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Hexadecanoic acid	High	Yes	No	Yes	No	Yes	No	No	-2.77
Terpinen-4-ol	High	Yes	No	No	No	No	No	No	-4.93
Sabinene	Low	Yes	No	No	No	No	No	No	-4.94
Beta-selinene	Low	No	No	No	Yes	Yes	No	No	-3.68
Curzerene	High	Yes	No	No	Yes	Yes	No	No	-4.32
Germacrene B	Low	No	No	No	No	Yes	No	No	-3.45
Myrcenol	High	Yes	No	No	No	No	No	No	-5.1
Spathulenol	High	Yes	No	No	Yes	No	No	No	-5.44
Azithromycin	Low	No	Yes	No	No	No	No	No	-8.01
Hydroxychloroquino ne	High	No	No	No	No	No	No	No	-7.4
Ivermectin	Low	No	Yes	No	No	No	No	No	-7.14
Remdesivir	Low	No	Yes	No	No	No	No	Yes	-8.62

Table 8: Drug likeliness of all the active compounds of *Shailam* predicted from SwissADME

Molecule	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score
Eugenol	0	0	0	0	1	0.55
Caryophyllene	1	0	0	0	1	0.55
Amrinone	0	0	0	0	1	0.55
Phytol	1	1	1	1	2	0.55
2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	0	0	0	0	1	0.55
1,5-Hexadiyne	0	3	0	0	2	0.55
Isopinocarveol	0	1	0	0	2	0.55
Di-n-Decylsulfone	1	1	1	1	2	0.55
1,8-cineole	0	1	0	0	2	0.55
Aspidospermidin-17-ol	0	0	0	0	0	0.55
N,N’Dibenzylidene-3,3’-dichlorobenzidine	1	1	0	1	1	0.55
Linolenic acid	1	1	1	0	1	0.85
Hexadecanoic acid	1	0	1	0	1	0.85
Terpinen-4-ol	0	1	0	0	2	0.55
Sabinene	1	1	0	0	2	0.55
Beta-selinene	1	0	0	0	2	0.55
Curzerene	0	0	0	0	1	0.55
Germacrene B	1	0	0	0	2	0.55
Myrcenol	0	1	0	0	2	0.55
Spathulenol	0	0	0	0	1	0.55
Azithromycin	2	3	1	1	3	0.17
Hydroxychloroquinone	0	1	0	0	0	0.56
Ivermectin	2	4	1	1	4	0.17
Remdesivir	2	3	2	1	3	0.17

Table 9: Medicinal Chemistry Properties of Phytoconstituents of *Shailam* predicted from SwissADME

S.No	Molecule	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic accessibility
1.	Eugenol	0	1	1	1.58
2.	Caryophyllene	0	1	2	4.51

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3.	Amrinone	0	0	1	2.04
4.	Phytol	0	1	2	4.3
5.	2-(2,5-Hexadiynyloxy)tetrahydro-2H-pyran	0	1	1	4.17
6.	1,5-Hexadiyne	0	1	1	3
7.	Isopinocarveol	0	1	1	3.7
8.	Di-n-Decylsulfone	0	0	2	4.16
9.	1,8-cineole	0	0	1	3.65
10.	Aspidospermidin-17-ol	0	0	1	5.8
11.	N,N'Dibenzylidene-3,3'-dichlorobenzidine	0	1	2	3.15
12.	Linolenic acid	0	1	2	3.03
13.	Hexadecanoic acid	0	0	2	2.31
14.	Terpinen-4-ol	0	1	1	3.28
15.	Sabinene	0	1	1	2.87
16.	Beta-selinene	0	1	2	3.42
17.	Curzerene	0	1	2	4.05
18.	Germacrene B	0	1	2	3.65
19.	Myrcenol	0	1	1	2.2
20.	Spathulenol	0	1	1	3.78
21.	Azithromycin	0	0	2	8.91
22.	Hydroxychloroquinone	2	1	0	3.34
23.	Ivermectin	0	1	3	10
24.	Remdesivir	0	1	2	6.33

Conclusion

The *In silico* molecular docking study of *Shailam's* phytoconstituents against the SARS-CoV-2 Spike Protein (PDB ID 7DDD**)** shows docking score ranging from 3.8 to 8.8**.** The compounds such as Aspidospermidin-17-ol, N,N'Dibenzylidene-3,3'-dichlorobenzidine bind effectively to the active spot region of SARS-CoV-2 Spike Protein (PDB ID 7DDD**).** ADME analysis predicts that all of *Shailam's* phytocompounds meet four Lipinski's rule of five and has a higher bioavailability score (0.55) as compared to standard conventional drugs, Twelve of *Shailam's* phytochemical compounds have high GIT absorption and can cross the blood–brain barrier (BBB). This information obtained can be used as a primary tool for the evaluation of interventional drug in pharmacodynamic studies, *in vitro, in vivo* studies, randomized clinical trials, etc.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Rajalakshmi S, Samraj K, Sathiyarajeswaran P, Kanagavalli K. Preparedness of Siddha System of Medicine in Practitioner Perspective during a Pandemic Outbreak with Special Reference to COVID-19. Cell Med. 2020; 10(4):1–6.
2. COVID-19 cases by country worldwide 2021 | Statista [Internet]. [cited 2022 Mar 17]. Available from: https://www.statista.com/statistics/1111696/covid19-cases-percentage-by-country/
3. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2022 Mar 17]. Available from: https://covid19.who.int/
4. When will coronavirus end? WHO chief has a simple answer [Internet]. [cited 2021 Aug 18]. Available from: https://www.livemint.com/
5. *Shailam* [Package insert]. Chennai: LINCS Pharmaceuticals; 2021.
6. Jayashree T and Subramanyam C. Antiaflatoxigenic activity of eugenol is due to inhibition of lipid peroxidation. Lett Appl Microbiol. 1999; 28(3):179-183.
7. Maralhas A, Monteiro A, Martins C, Kranendonk M, Laires A, Rueff J, Rodrigues AS Genotoxicity and endoreduplication inducing activity of the food flavouring eugenol. Mutagen. 2006; 21(3):199-204.
8. Wang C, Zhang J, Chen H, Fan Y, Shi Z. Antifungal activity of eugenol against Botrytis cinerea. Trop Plant Pathol. 2010; 35(3):137-143.
9. Moo CL, Yang SK, Osman MA, Yuswan MH , Yan Loh JY , Lim WM , Lim SH , Lai KS Antibacterial activity and mode of action of β-caryophyllene on Bacillus cereus. Polish J Microbiol. 2020; 69(1):49-54.
10. Dahham SS, Tabana YM, Ahamed MBK, Majid AMSA. In vivo anti-inflammatory activity of β-caryophyllene, evaluated by molecular imaging. Mol Med Chem. 2016:1-6.
11. De Oliveira CC, de Oliveira CV, Grigoletto J, Ribeiro LR , Funck VR, Grauncke ACB, de Souza TL , Souto NS, Furian AF , Alencar Menezes IR, OliveiraMS .

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Anticonvulsant activity of β-caryophyllene against pentylenetetrazol-induced seizures. Epilep Behav. 2016; 56:26-31.
12. Thomas CV. Amrinone Prevents The Inhibition Of Muscle Pyruvate Dehydrogenase Complex Activity During Sepsis, Shock. 1996; 5(3):229-232.
13. Alousi AA, Farah AE, Lesher GY, Opalka CJ. Cardiotonic activity of amrinone - win 40680 [5-amino-3,4'-bipyridin-6 (1H)-one]. Circ Res. 1979; 45(5):666-677.
14. Islam MT, Ayatollahi SA, Zihad SMNK, Phytol anti-inflammatory activity: Pre-clinical assessment and possible mechanism of action elucidation. Cellul Mol Biol. 2020; 66(4):264-269.
15. Gupta K, Taj T, Thansiya B, Kamath JV. Pre-clinical evaluation of hepatoprotective activity of phytol in wistar albino rats. IP Int J Compr Adv Pharmacol. 2019; 4(1):17-20.
16. Juergens LJ, Worth H, Juergens UR. New Perspectives for Mucolytic, Anti-inflammatory and Adjunctive Therapy with 1,8-Cineole in COPD and Asthma: Review on the New Therapeutic Approach. Adv Ther. 2020; 37(5):1737-1753.
17. Murata S, Shiragami R, Kosugi C, Tezuka T, Yamazaki M, Hirano A, Yoshimura Y, Suzuki M, Shuto K, Ohkohchi N, Koda K. Antitumor effect of 1, 8-cineole against colon cancer. Oncol Rep. 2013; 30(6):2647-2652.
18. Singh S, Nair V, Jain S, Gupta YK. Evaluation of anti-inflammatory activity of plant lipids containing α-linolenic acid. Indian J Exp Biol. 2008; 46(6):453-456.
19. Xu MQ, Hao YL, Wang JR, Li ZY, Li H, Feng ZH, Wang H, Wang JW, Zhang X. Antitumor activity of α-linolenic acid-paclitaxel conjugate nanoparticles: In vitro and in vivo. Int J Nanomed. 2021;16:7269-7281.
20. Jung SW, Thamphiwatana S, Zhang L, Obonyo M. Mechanism of antibacterial activity of liposomal linolenic acid against helicobacter pylori. PLoS One. 2015; 10(3):1-13.
21. Cartron ML, England SR, Chiriac AI, Josten M, Turner R, Rauter Y, Hurd A, Sahl HG, Jones S, Foster SJ. Bactericidal activity of the human skin fatty acid cis-6-hexadecanoic acid on *Staphylococcus aureus*. Antimicrob Agents Chemother. 2014;58(7):3599-3609.
22. Walton SF, McKinnon M, Pizzutto S, Dougall A, Williams E, Currie BJ. Acaricidal activity of Melaleuca alternifolia (tea tree) oil: in vitro sensitivity of sarcoptes scabiei var hominis to terpinen-4-ol. Arch Dermatol. 2004 May;140(5):563-6.
23. De Sousa DP, Nóbrega FFF, De Morais LCSL, De Almeida RN. Evaluation of the anticonvulsant activity of terpinen-4-ol. Zeitschrift fur Naturforsch - Sect C J Biosci. 2009; 64(1-2):1-5.
24. Schmidt E, Wanner J, Hiiferl M, Jirovetz L, Buchbauer G, Gochev V, Girova T, Stoyanova A, Geissler M. Chemical composition, olfactory analysis and antibacterial activity of Thymus vulgaris chemotypes geraniol, 4-thujanol/terpinen-4-ol, thymol and linalool cultivated in Southern France. Nat Prod Commun. 2012; 7(8):1095-1098.
25. Nunes TAL, Santos MM, de Oliveira MS, de Sousa JMS, Rodrigues RRL, Sousa PSA, de Araújo AR, Pereira ACTDC, Ferreira GP, Rocha JA, Rodrigues Junior V, da Silva MV, Rodrigues KADF. Curzerene antileishmania activity: Effects on Leishmania amazonensis and possible action mechanisms. Int Immunopharmacol. 2021; 100:108130.
26. Dzul-beh ADJ, García-sosa K, Uc-cachón AH, Bórquez J, Loyola LA, Barrios-García HB, Peña-Rodríguez LM, Molina-Salinas GM. In vitro growth inhibition and bactericidal activity of spathulenol against drug-resistant clinical isolates of *Mycobacterium tuberculosis*. 2019; 29:798-800.
27. Francisca I, Borges DJ, Lopes T, Calixto D, Pereira SV, Paleo Konno R, Corrêa Pinto TU, Wanderley Tinoco S, Lasunskaia L, Ramos Leal E, Frazão Muzitano IC, Michelle, Anti-mycobacterial and immunomodulatory activity of n -hexane fraction and spathulenol from Ocotea notata leaves. Rodriguésia , 2021; e01162019:1-14.
28. Jemal K. Molecular Docking Studies of Phytochemicals of Allophylusserratus Against Cyclooxygenase-2 Enzyme. bioRxiv. 2019; 11:2–8.
29. Karpiński TM, Kwaśniewski M, Ożarowski M, Alam R. In silico studies of selected xanthophylls as potential candidates against SARS-CoV-2 targeting main protease (Mpro) and papain-like protease (PLpro). Herba Pol. 2021; 67(2):1–8.
30. Swiss Institute of Bioinformatics [Internet]. [cited 2022 Apr 18]. Available from: http://www.swissadme.ch/
31. Kehinde I, Ramharack P, Nlooto M, Gordon M. The pharmacokinetic properties of HIV-1 protease inhibitors: A computational perspective on herbal phytochemicals. Heliyon. 2019; 5(10):e02565.
32. Gao Y, Gesenberg C, Zheng W. Oral Formulations for preclinical studies: Principle, design, and development considerations. Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice: Second Edition. Elsevier Inc.; 2017. 455–495 p.
33. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017; **3(7)**: 42717.
34. Hess-Fischl A. Handbook of Drug-Nutrient Interactions, (2nd Ed.)Humana press 2010. 120-121p.
35. Dong X, Zhang Z.M, Liu F, Wancen Yu, Lin F, Yanhao, Jiang H.Y, Zhenyu H. Genesis of the metamorphic rock from southeastern Lhasa terrane and the Mesozoic-Cenozoic orogenesis. Acta Petrol Sin. 2012; 28(6):1765–1784.

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