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In-silico Study to Elucidate Corona Virus by Plant Phytoderivatives that Hits as a Fusion Inhibitor Targeting *HR1* Domain in Spike Protein Which Conformational Changes Efficiently Inhibit Entry COVID-19

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Abstract

Introduction: COVID-19 could be a human beta corona virus that have potential source of severe widespread respiratory and asymptomatic multiple pathophysiological conditions and is belonging to the SARS and MERS β-corona viruses linage that have inflated mortality rates and acute potential of pandemic. The viral envelope surface spike glycoprotein (S) binding with host cell receptor angiotensin-converting enzyme 2 (ACE2) and conciliate fuse the virus particle inside the host cell membranes, promising spike protein substantially important to endocytosis and host species an involuntary orienting response.

Methods: Within the present *in-silico* study, two plant bioactive compounds namely ALS-1 and ALS-2 (from *Alangium salvifolium*) were analyzed for his or her inhibitory role on fusion peptide region or S2 HR-1 domain and efficiently block virus entry into host cell by applying the molecular simulation, docking studies. Other parameters viz. determination of molecular interaction-based binding affinity values, protein-ligand interactions, Lipinski rule of 5, functional properties and biological activities for the above compounds were also calculated by employing the acceptable bioinformatics tools.

Results: The results of docking analysis clearly showed that ALS-1 has highest binding affinity with trimeric Spike glycoprotein (-11.6 kcal/mole) and ALS-2 (-10.8 kcal/mole). Based on protein interaction analysis both phytoderivatives bind HR-1 (fusion peptide) domain. Other parametric results showed good absorption activity and not violated Lipinski score of drug-likeness.

Conclusion: Therefore studied plant derivatives may have the potential to play a big role as 2019 n-CoV fusion peptide inhibitor, revealing influential inhibitory activity against S-participated endocytosis and 2019 n-CoV viral infection, suggesting further optimizations (3-DQASR) and pharmaceutical development of both derivatives, respectively, to stop and treat novel COVID-19 infection.

Keywords: novel Corona Virus (2019nCOV); Spike glycoprotein; Fusion peptide; Lead Molecules; Fusion inhibitor

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Introduction

Outburst of the novel corona virus that appear within the central Chinese city of Wuhan in late December are being sign on daily round the world. Quite 3,23,256 people have died from (COVID-19), the disease originated by the novel corona virus, while some 4.9 million infections are reported in additional than 185 countries and territories [1]. Approximately quite 1.3 million people have recovered so for. Severe acute respiratory syndrome corona virus (SARS-CoV) rose in humans from an animal reservoir in 2002 and swiftly spread globally causing 8,096 cases and 774 associated mortality in 26 countries through July 2003 [2]. SARS-

CoV again in a very small epidemic in 2004, but has since vanish from human circulation. Like severe acute respiratory syndrome (SARS)-CoV, COVID-19 similar to lineage B β-corona virus, and it's the aptitude to acknowledge human cell surface protein angiotensin-converting enzyme-2 (ACE2) and as a receptor to infect host cells [3,4]. Corona viruses are round shaped or idiomatic, with a diameter of 80-120 nm. While examining under the electron microscope, the virion surface is trim with club-like ledge assembled by the trimeric (mushroom) like spike (S) glycoprotein. The viral capsid is surrounded by the membrane (M) glycoprotein, the foremost abundant structural protein that embeds within the envelope via three transmembrane domains. Supplementary, a small trans-membrane protein called the envelope (E) protein is also present in a very few amounts within the envelope [5-8]. The nucleocapsid (N) protein binds to the RNA genetic material in a very beads-on-a-string fashion, forming the helical symmetrical nucleocapsid. The corona virus genome could be a positive-sense, non-segmented, single-stranded RNA, with startle large size scale from 27 to 32 kb. Corona virus central dogma is initiated by the binding of Spike glycoprotein protein to the cell surface receptor (s). The Spike protein is distinguished of two functional subunits, S1 (bulb) for receptor binding and S2 (stalk) for membrane fusion. Determined interaction between S1 and therefore the cognate receptor depart an extreme conformational change within the S2 subunit, prime to the fusion between the virus envelope and therefore cellular membrane and release of the nucleocapsid into the host cytoplasm. SARS-CoV spike (S) protein S2 subunit plays an essential role in conciliating virus fusion with and entry into the host cell, during which the heptad repeat-1 (*HR1*) and heptad repeat 2 (*HR2*) can merged to make six-helical bundle (6-HB), thereby cross-over viral and cellular membranes in close proximity for fusion, whether a COVID-19 Spike-*HR1* can also function a vital target for the event of COVID-19 fusion/entry inhibitors [9-11]. The aim of the present study was to estimate the inhibitory and interaction analysis of virus spike glycoprotein (S) with *Alangium salvifolium* phyto-derivatives **(Figure 1)** [12] by usage of various bioinformatics tools.

Materials and Methods

Ligand preparation

The lead compounds were collected from an editorial published by Suresh Shravya and his coworkers [13]. The compounds were selected from Salviifoside derivatives from the genus *Alangium*, especially from the *A. salvifolium* plant. Chemical structure of

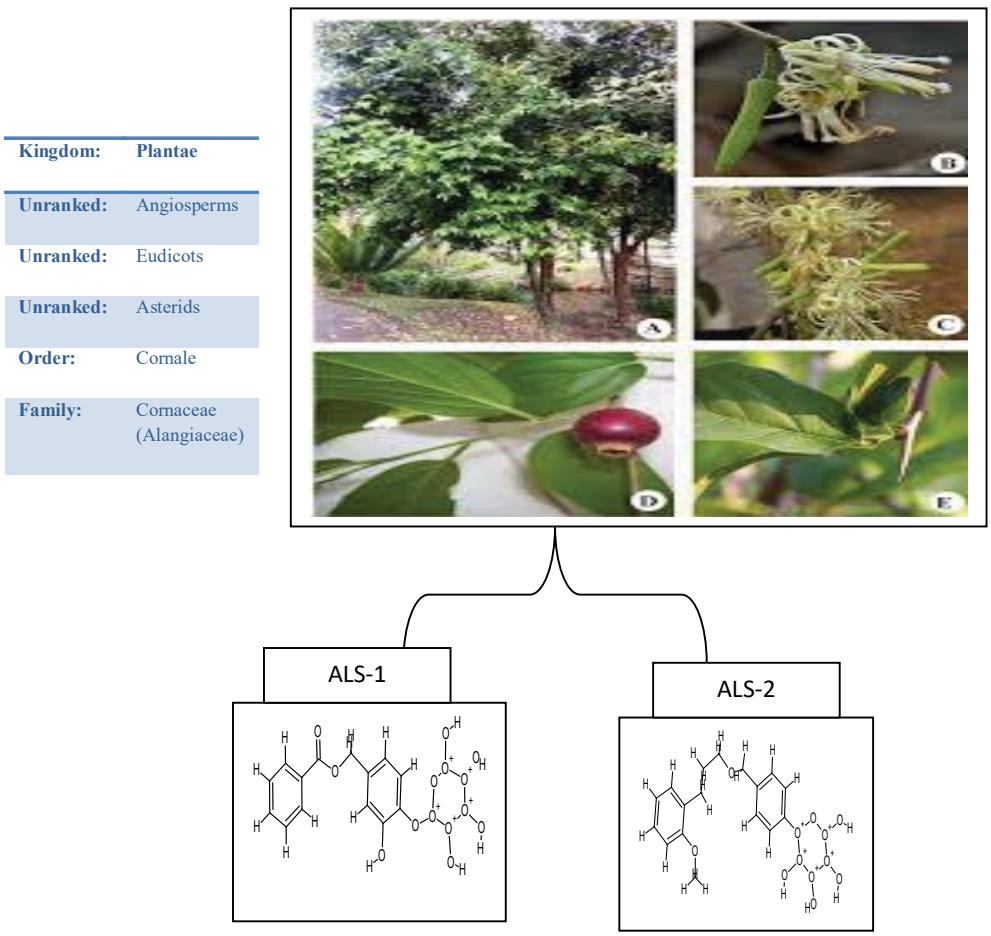

Figure 1 Medicinal plant and phyto derivatives images and structures.

Alangium salvifolium plant derivatives ALS-1 and ALS-2 were drawn with the using of CHEM-sketch software with possible structure definition file format for docking (Chem-Sketch-www.acdlabs.com/download/), an absolutely strapping chemical structure drawing program [14]. The chem.-sketch file format.sk1 converted to mol. file for further ligands physical characterization by using Pymol, arguslab, and online pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction_single) software.

Retrieve receptor protein

Protein Data Bank (PDB) is that the worldwide database of structural and observational data of biological macromolecules, established in Brookhaven National Laboratories. It collected structural and observational data of the macromolecules specially protein data which retrieved by the X-ray crystallographic and NMR methods. 3D structure of trimeric mushroom like virus Spike glycoprotein from PDB, whose PDB ids is 5wrg respectively [15].

Molecular docking and simulation

The protein atoms were typed using the CHARMm field of force. The site of the protein was first identified and defined using an eraser size 10.0 Aº. Molecular docking studies on the above mentioned selected phytoderivatives against virus spike (S) protein (5wrg) was drained in Autodock (vina) in PyRx-phython prescription 0.8, which is freely accessible and designed for molecular docking studies. Autodock-PyRx includes docking sorcerer with an easy-to-use programme which makes it a potential tool for computer-based drug design. Autodock (Vina) PyRx even have facility to chemical spreadsheet-like functionality and powerful visualization engine that are must for cogent drug design [16]. The chosen drug targets were energy minimized, and converted them into pdbqt file format in Autodock-PyRx. Then the ligands were docked into the site of receptor using Pyrx (Autodock) dock procedure. Affinity of binding energy score absolute energy was obtained from the results. Ligand drug potential ability was through with the ARGUSLAB software (ArgusLab-www.arguslab.com/), during which the result is being obtained on the premise of pose energy. Before docking a molecule, first it's needed to define the atoms that conjure the Ligand like drug, inhibitor, etc., and therefore the Binding Site on the protein where the drug binds. The ultimate results are supported the sort of calculation we run like as Geometry optimization-search for 'Final Geometry' and Electronic spectra-search for 'Excited state properties'

Receptor-ligand binding analysis

Structure of Plant phytoderivatives open with saved pdb file format were upload in Discovery-studio 4.1 version. Use of protein-interaction tool, the binding pattern of receptor and ligands studied and plot the 2-D receptor -ligands graph for amino acid residue and bond formation between receptor pocket molecule and ligand [17]. Auto dock vina generated docking pair of protein and ligands were saved in pdb format, and were visualized in Discovery studio [18] visualization tool i.e. python-enhanced molecular graphics tool. It excels at three-dimensional visualization of proteins, small molecules, density, surfaces and trajectories. It also includes molecular editing, ray tracing, and movies. The ligand binding sites and surrounding amino acids of ligands were also visualized. Molecular interactions within the sort of hydrogen bonds between proteins and ligands were characterized and therefore the distance of hydrogen bonds was also calculated. Site Prediction proteins have specific sites, the residue side chains that form a full of life cavity or cleft where the ligands or atoms or other proteins are capable to bind and are called active sites.

In-silico pharmacokinetic prediction study

Pharmacokinetic (ADMET) properties that's Absorption, Distribution, Metabolism, Execration and Toxicity value were examine by using of Admet-SAR and Online swissPort database which provides latest and most inclusive manually created data for various chemicals with known ADMET properties that helpful to pharmacological properties of studied molecule [19]. Predictions of drug properties were calculated in Swissport, an online based pharmacokinetic tool. It determines lipinski rule of 5 (rule of five), an essential to judge drug likeness or determine the chemical compounds pharmacological and biological properties, which concur with the oral prescribed drugs for human [17]. The rule of five values includes cLog P, mass, bond donors and bond acceptor for the drugs. Further, we predicted compounds activity on biological targets (kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor)

Results and Discussion

There were various crystal structures cited within the Protein Data Bank (PDB) (www.rcsb.org/pdb) on Spike trimer protein. During this study (PDB ID: 5 wrg) with 2.1 Å resolution Spike glycoprotein trimer (mushroom like) protein structure **(Figures 2a, 2b and 2c)** molecular docked with Phyto-derivatives of *Alangium salvifolium*. The reference ligands were docked into the pocket site of the Spike glycoprotein (S) assembly, and also the docking score was found in rage of -11.6 Kcal/mol and -10.8 kcal/mol with % RMSD value **(Table 1).** The ultimate trajectory files were taken for calculating the receptor-ligands of the complex structures. At the identical time as running receptor-ligand interaction analysis. 2D-Diagram plot shows the steadiness of the complex structures. Interaction analysis clearly marked that phytoderivatives intercept region of for fusion peptide region and HR-1, and interlock between all monomer **(Table 2 and Figure 3).** previous study the functional domain in (SARS)-CoV, Spike protein, counting N-terminal domain (14-305aa),receptor-binding domain (319-541aa), and receptor-binding motif (437-508aa) in S1 subunit which including 14-685aa and fusion peptide (788-806aa), Heaped region HR-1 (912-984aa), *HR2* (aa1163-1213aa), trans-membrane domain (1214-1237aa) and cytoplasm domain (1238-1273aa) in S2 subunit range between 686-1273 residue **(Figure 2e).** In the post-fusion hairpin conformation of the SARS-CoV or MERS-CoV S protein, the *HR2* domain forms both rigid helix and elastic or versatile loop to interact with *HR1* region [19]. There are many well built interactions between *HR1* and *HR2* domains inside the helical region, which is thus designated "fusion core domain" (*HR1* and *HR2*core domain, respectively). Conforming to the sequence alignment, the COVID-19 and SARS-CoV S2 subunits

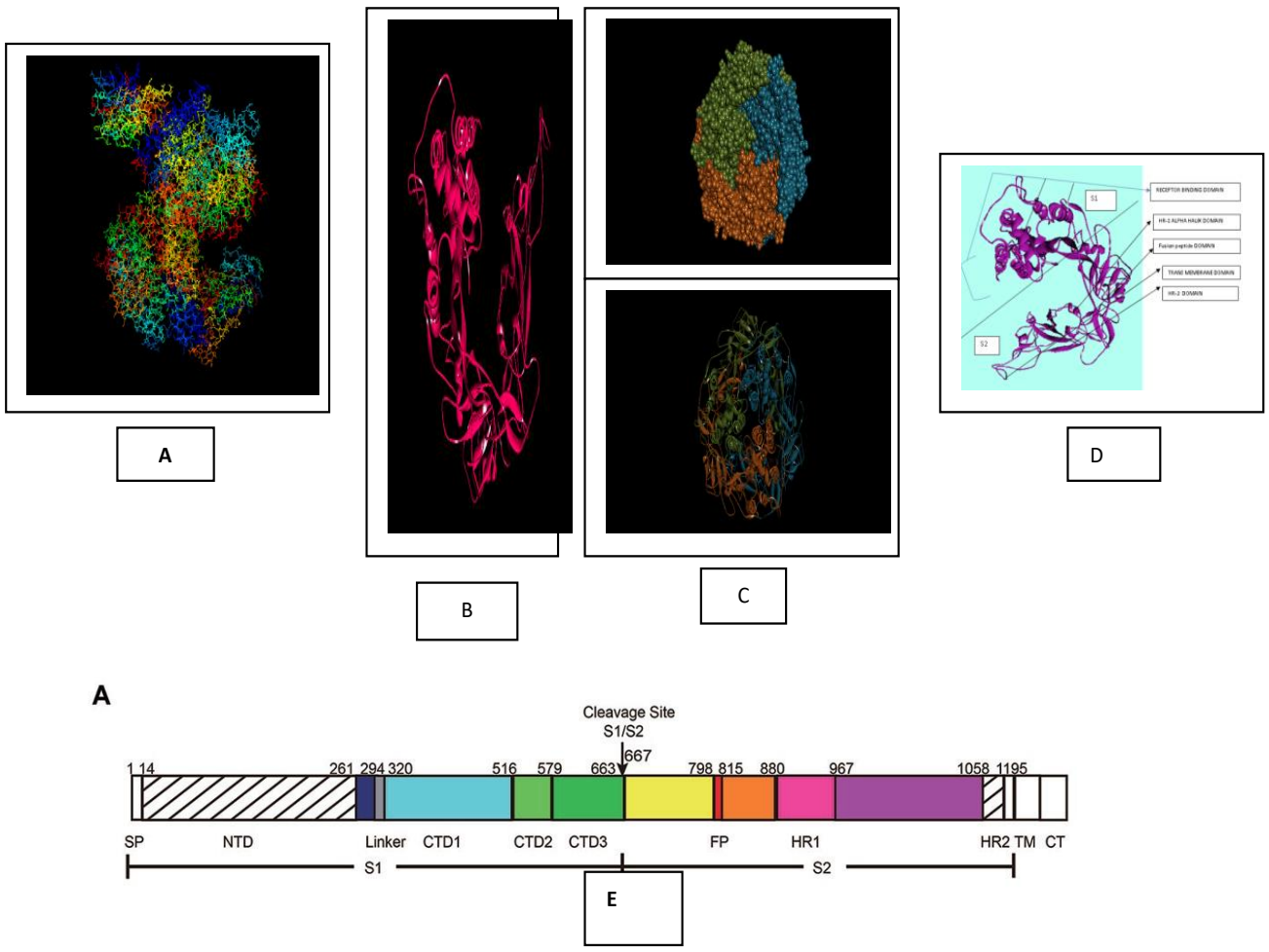

Figure 2 Virus spike protein (A) Ismetric view (B) Monomer spike protein (C) Trimer spike protein (D) Spike protein domain determination (E) Spike protein ray amino residue mapping.

Table 1 Different chemical and physiological properties of phyto-derivatives of *Alangium salvifolium* studied medicinal plants (recognized as a ligands).

S. No	Ligands code	IUPAC name	Chemical name	Molecular weight	Element involve in docking	Molar refractivity	Molecular formula	Number of heavy atoms	Num of H bond acceptor	Num of bond donar	Solubility
1	ALS-1	4 (benzoyloxy) methyl -2hydroxyphenoxy tetrahydorxy hexoxone 1, 2, 3, 4, 5, pentaium	Salviifoside-A	437.32	AC HD OA	81.88	$C_{16}H_{21}O_{14}$	28	4	5	Hydrophilic
2	ALS-2	-----	Salviifoside-B	419.35	AC HD OA	94.46	$C_{17}H_{23}O_{12}$	29	12	4	Hydrophilic

Table 2 Mean values of docking energies (kcal/mol) and standard deviation for each skeletal type of *Alangium salvifolium* phyto-derivatives as ligands with virus spike (S) protein targets.

Target Receptor	Ligands	Dimension Centre (x=25, y=25, z=25	No of pose	RMSD % Lower	RMSD % Upper	Mean binding energy
Virus Spike protein trimer (Mushroom like) structure (PDBID-5wrg)	ALS- 1	X=190.072, y=190.525 Z=167.9877	8	55.21	44.62	-11.6
	ALS-2		8	63.44%	39.27%	-10.8

are highly conserved, with 92.6% and 100% overall identity in fusion core domain. However, inside the *HR1*core region, out of 21 residue only 8 residue show mutation (~38% diversity). This is significantly different from the *HR1*core region of previously identified SARS-like viruses, like WIV1, Rs3367, and RsSHC014, which are 100% clone of that of SARS-CoV [20]. These novel point mutations in COVID-19, S2 subunit may change the interaction pattern between fusion core domains within the post-fusion core, thus affecting the helical bundle (6-HB) construction supported our past experience. But *Alangium salvifolium* phyto-molecule bind diversely monomer_A (738-976) monomer_B (951-988) and monomer_c (741-987) that cover fusion peptide to fusion core domain (FP, *HR1*) derived peptides region, respectively **(Table 3 and Figure 3)** and explored their bond interaction characteristics. It gives more satisfaction just in case of mutation because studied molecule bind altogether three monomer give more surety to inhibit the targeted region. Since the fusion core domain and S-Hepated region residue 100% inhibit /block, with *Alangium salvifolium* phytoderivatives may act as a fusion inhibitor in much the identical way as reported SARS-CoV fusion inhibitor [4,20,21]. These result confirm, for the primary time, that ALS-1 and ALS-2 are ready to interact with fusion peptide region and HR-1 conserved region that affecting the 6-HB formation therefore inhibit COVID-19 fusion with the host cell, as past studies confirmed that in SARS-CoV, MERS-CoV, and other HCoV [4,5,20,21]. When S1 subunit recognizes its receptor on host cell,

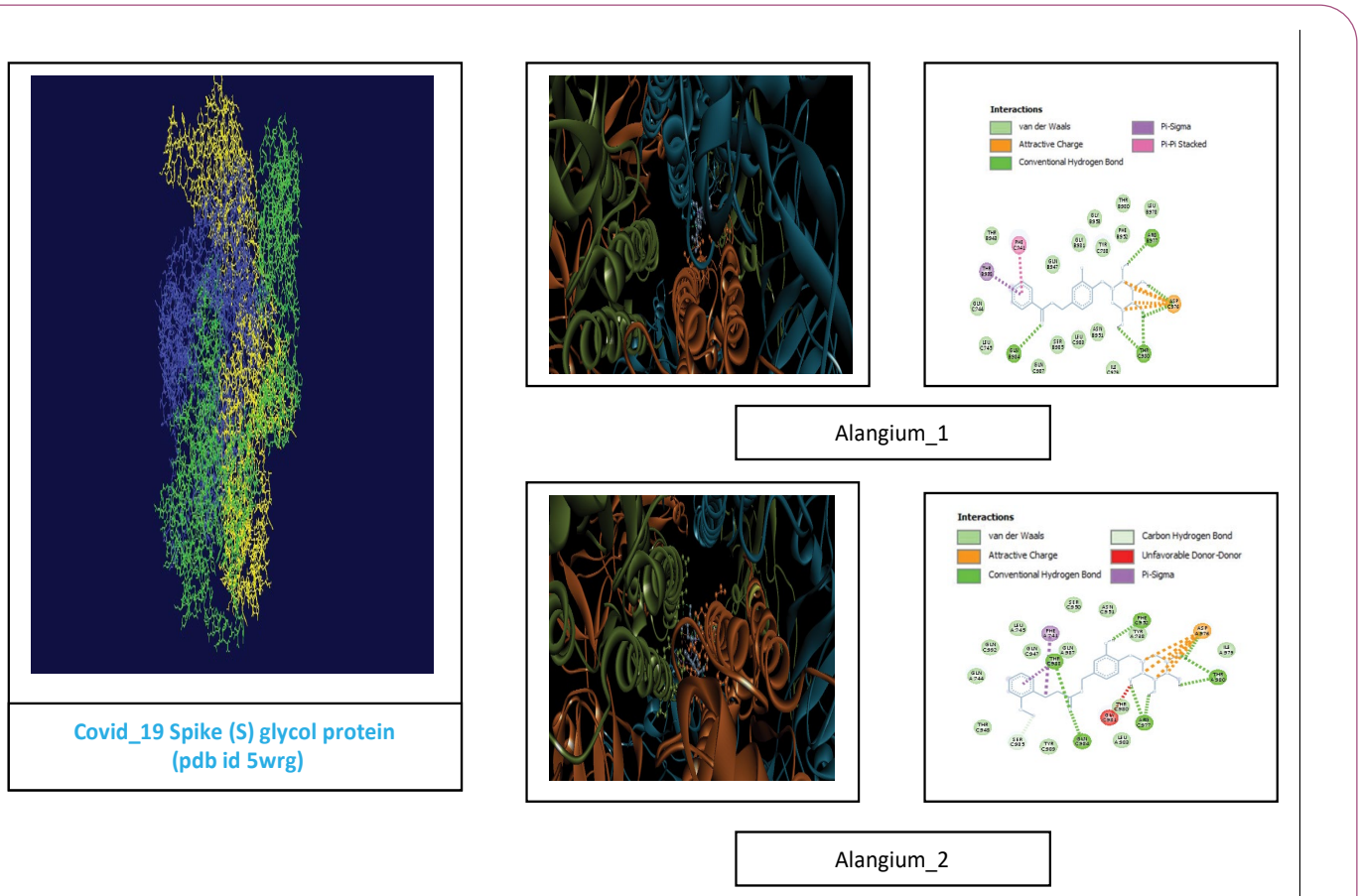

Figure 3 Interaction study Visualize binding modes of ligand molecules within the binding pocket of receptor and interactions of top two docking score ligands molecules with COVID_19 spike trimer glycoprotein (PDB_5wrg).

Table 3 The binding interactions analysis of Virus Spike (Receptor) protein with *Alangium salvifolium* phyto-derivatives (ligands).

Target Receptor	Ligands	Number of pose	Number of chain involve in pocket	Number of amino acid involve in active site (Bond formation) (chain name and residue number)
Virus Spike Protein (Trimer) Assembly	ALS-1	8	2	C-ASP (976), C-THR (980), C-ILE (979), B-ASN (951), C-LEU (983), B-SER (985), C-GLN (987), B-GLN (984), C-LEU (745), C-GLN (744), B-THR (988).B-THR943), C-PHE (741) B-GLN (947), B-GLY (981, B-GLY (953), C-TYR (738), B-PHE (952), B-THR (980), B-LEU (978), B-ARG (977)
	ALS-2	8	2	A-ASP (976), A-ILE (979), A-THR (980), C-ARG (977), C-THR (980), C-GLY (981), C-ARG (977), A-LEU (983), C-GLN (984), C-TYR (989), C-SER (985), C-THR (943), A-GLN (992), A-LEU (745), C-PHE (741), C-THR (988), A-GLN (987), C-SER (950), C-ASN (951), C-PHE (952), A-THR (738)

the fusion core domains are exhibited and merged with one another, forming 6-HB to participate in endocytosis initiation between virus and host cell [22]. Notably, both ALS-1, ALS-2 fusion core inhibitor, exhibited potent inhibitory activity against Spike protein involved endocytosis. Phytoderivatives which play a pivotal role to inhibit fusion core domain may have a possible to drug against COVID-19. Next step to optimization of drug development step pharmacological evaluation prediction required for qualifying active pharmacological ingredients (API). Therefore, Pharmacological evaluation of phyto-derivatives ALS-1 and ALS-2 were evaluated for ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicology) properties and drug likeliness.

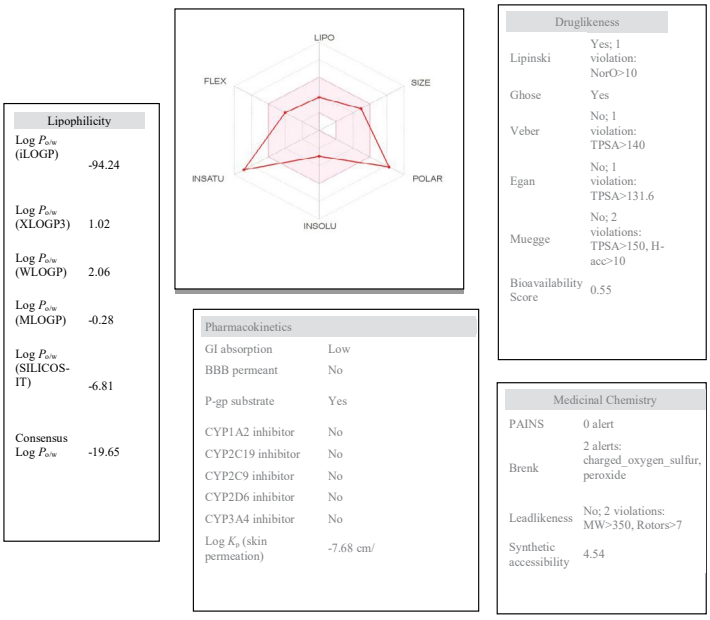

Figure 4 ADMET properties of ALS-1 phytocompounds identified in *Alangium salvifolium*.

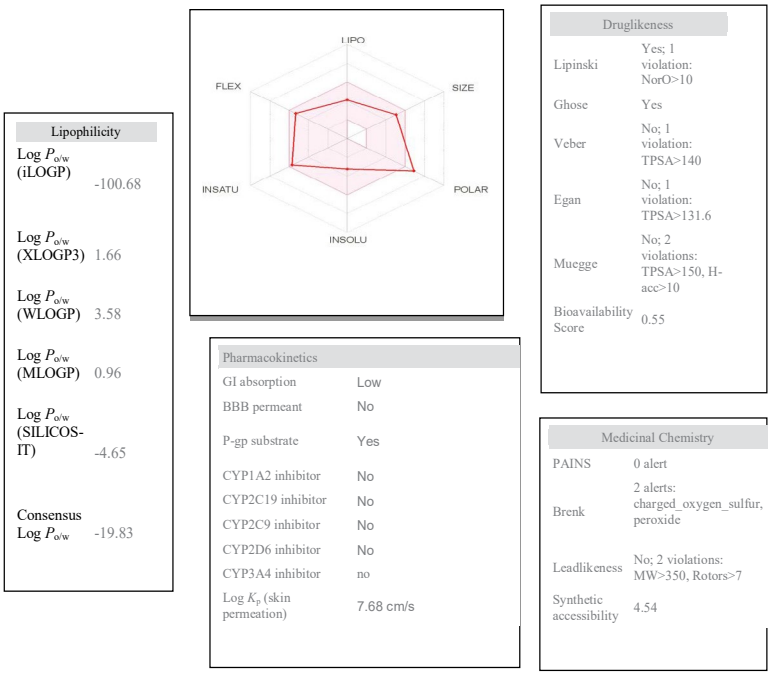

Figure 5 ADMET properties of ALS-2 phytocompounds identified in *Alangium salvifolium*.

Both were found to best interaction with virus Spike glycoprotein and violate the Lipinski's rule. Both phyto-derivatives were screened on the premise of BBB permeability, GI absorption, with optimum solubility, Toxicity and carcinogenic tests screened the compounds and ultimately, both phyto-derivatives, drug-like, having suitable ADMET depicted in **Figures 4 and 5**.

Conclusion

Hence, we conclude that the *Alangium salvifolium* phyto-derivatives may have suitable potential, neither inhibits the virus fusion nor blocks the massive conformation changes by interaction between HR-1 and fusion peptide junction. This study suggests that the chosen phytoderivatives will be further optimized and fine investigated and evaluated for active pharmaceutical ingredients (API) or whenever drug goes under lab and run phases, we may be able to use as *Alangium salvifolium* crude extract to prevent and treat COVID-19 infection.

Conflicts of Interest

The authors have declared that no conflict of interest exists

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