A rational drug designing: What bioinformatics approach tells about the wisdom of practicing traditional medicines for screening the potential of Ayurvedic and natural compounds for their inhibitory effect against COVID-19 Spike, Indian strain Spike, Papain-like protease and Main Protease protein

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Abstract

The new outbreak of Coronavirus disease (COVID-19) has been entitled as a pandemic by W.H.O. It spreads to almost 211 countries due to its contagious nature. There is an urgent need for developing specific therapeutic agents against COVID-19. We have performed virtual screening of 52 ligands; most of which are essential components of traditional Ayurvedic medicine as well as natural compounds and three were standard repurposing drugs against COVID-19 Spike, Indian strain Spike (IS-Spike), PL-Pro and M-Pro to find potential inhibitor effects. Based on the docking results, it is estimated that compounds have a better binding affinity with M-Pro and PL-Pro than Spike as well as IS-Spike so it can be beneficial as therapeutics against COVID-19. We also conclude that the binding affinity of ligands with IS-Spike gets low as compared to Spike so the inhibitory potential of drugs may get weak. Based on the calculation of average binding energy (B.E) with the three targets, Spike, PL-Pro, and M-Pro, we found10 best ligands viz. (1) Punicafolin (2) Emblicanin A (3) Punigluconin (4) Lopinavir (5) Kuwanon X (6) Rutin (7) Lithospermic Acid (8) Phyllanemblinin A (9) Amarogentin and (10) Amaroswerin for inhibition. These ligands may act as potential inhibitors against COVID-19 druggable tri-targets. Network analysis revealed that four ligands out of 10 leading compounds are common in all four different networks (Spike, IS-Spike, PL-Pro, and M-Pro) which come under *Phyllanthus emblica*. Notably, a compound of *Azadirachta indica* out of 4 and a single compound of *Swertia chirata* was found common in all networks. Additionally, a standard drug Lopinavir and a compound of *Salvia miltiorrhiza* are frequently found in all networks. In principle, it appears plausible that the compounds which are common in the entire network should have more inhibitory potential against COVID19 due to the better binding potential among all targets, thus providing better candidacy for drug development.

Introduction

Another episode of pneumonia brought about by novel corona virus disease (COVID-19) of obscure aetiology, which first time rose in Wuhan, China toward the end of December 2019 with exceptionally infectious virus (human to human) **[1].** This virus has affected numerous peoples of China and now it spreads around 211 countries in very short duration and it becomes pandemic. COVID-19 has been announced as a general wellbeing crisis of worldwide worry by the World Health Organization **[2].** Phylogenetic evolutionary analysis revealed that the COVID-19 have 79% nucleotide homology with SARS-CoV, 96% nucleotide homology with bats SARS-CoV and 50% identity with MERS- CoV **[3], [4]**.

Although specific vaccines and antiviral operators are the highly effective strategies to forestall and treat viral disease, no viable medications are available till datethat focus on the COVID-19 infections **[5]**. Currently Hydroxychloroquine and azithromycin used as a treatment of COVID- 19 **[6].** Some antiviral drugs like Favinapir, Ritoavir, Oseltamivir, Lopinavir, Ganciclovir and Remdesivir are clinically tested against COVID-19 infection **[7]**. According to the World Health Organisation, there are eight corona virus vaccines candidates those enter for human trials and 100 are in pre-clinical stage. Development of this therapeutics or vaccines may require months or years. Mean while an immediate therapeutics or control mechanism should therefore be actively searched.

In several countries like in India those have insufficient modern medical resources have rich resources of medical plants and those have been continued in practice in the treatment of different diseases. In fact, employments of conventional drugs are primarily supported in the majority of the world's population **[8]**.One of the significant motivations to separate and procedure conventional restorative compounds from plants are in rising practice because of their least side effect than other allopathic prescriptions **[9].** Ayurveda, the conventional Indian restorative framework remains the very ancient yet living customs with the sound philosophical and trial premise.The utilization of herbal treatment is equally significant in this Indian conventional arrangement of medication by the self-healing properties **[10]**. The adequacy of herbal treatment to control infectious illness was shown at some stage in the 2003 Severe Acute Respiratory Syndrome (SARS) flare-up **[11]**.

The COVID-19 encodes several proteins, some of which are essential to viral ingress and replication. Papain-like protease (PL-Pro), Main protease (M-Pro) and Spike protein are the best- contemplated proteins among them and make appealing focuses for the sedate turn of events. Coronavirus PL-Pro is a deubiquitinating protein that can reduce host anti-viral response by capturing the ubiquitin (Ub) framework. SARS PL-Pro divides ISG15 into two-domains, Ub-like protein, and Lys48-connected poly Ub chains, discharging di Ub Lys48 items **[12], [13].** SARS- 3CLpro or main protease (M-Pro) is a cysteine protease which is responsible for maturation of the polyproteins and essential to the lifecycle **[14]**. Spike (S) glycoprotein ties to the cell layer protein angiotensin-converting enzyme 2 (ACE2) to enter human cells. During the infectious condition, the S protein is severed into subunits, S1, and S2. However, S1 contains the receptor- binding domain (RBD) which permits corona viruses to legitimately tie to the peptidase domain (PD) of ACE2. In addition to S2 likely assumes a job in membrane layer combination **[15].** Mutational analysis of the COVID-19 genomes from different geographical location mainly India, Italy, USA, Nepal and Wuhan revealed a unique mutation found in spike surface glycoprotein (A930V) (24351C>T) in the Indian COVID-19 and it absent in other strains of different geographical origins **[16].**

Through Computational molecular virtual screening of small molecules from natural compounds, have been confirmed to directly inhibit these important proteins in SARS or Middle East respiratory syndrome (MERS) coronavirus **[17], [18], [19], [20], [21], [22].** Genome sequence analysis of COVID-19 revealed that the main proteins of COVID-19 have highest similarities with SARS-CoV and MERS-CoV **[3].**

Nucleozin is a compound, which found by arbitrary screening which actuates NP conglomeration, by repressing viral replication **[23]**. Several compounds from therapeutic plants have been accounted for to have antiviral bioactivities **[24], [25], [26]**.

In the current examination, we have completed the virtual screening of 52 ligands; the vast majority of which is a basic part of numerous traditional Ayurvedic medication just as others natural compounds and three of them are standard repurposing drugs against COVID-19 M-Pro, PL-Pro, Spike and IS-Spike to locate the potential inhibitors of its catalytic domain. In addition, three standard repurposing drugs utilizing nowadays against COVID19 infection strain proteins were likewise utilized for correlation through atomic docking. Furthermore we also compared the binding affinity of Spike and IS-Spike with ligands and evaluate the drug effectiveness and determination of their interaction pattern between them.The discoveries of this examination will prescribe different specialists with chances to distinguish the exact medication to battle COVID- 19.

Materials And Methods

Experimental investigation

With the purpose of analyzing the nature of molecular interaction of 52 ligands with their targets, the fundamental experimental approach involved retrieval of the accessible 3D structures of ligands and its targets along with the prediction of the unavailable structures of COVID-19 IS- Spike and PL-Pro. Docking analyses were carried out by HEX 8.0 and PatchDock Server. In addition, the docked complexes were visualized by Discovery Studio 3.5. A flowchart of the experimental design is delineated in Fig.1. The flow diagram shows the experimental approach and tools used to retrieve the 3D structure of targets, docking investigation, and representation of docked complexes.

Retrieval of ligands and target structures

The 3D structure of ligands was obtained from the PubChem Compound database, followed by its conversion from the SDF to PDB format. The molecular structures of Weddolactone and Desmethylweddolactone were modeled using ACD/Chem-Sketch because it was not available in PubChem database. Open Babel **[27]** was used for file format

conversion (.mol into pdb) and optimization of all ligands structure was done using Discovery Studio 3.5 (http://accelrys.com/products/collaborative-science/biovia-discovery-studio/visualization- download.php). The 3D structures of the COVID-19 Spike and M-Pro were retrieved from Protein Data Bank (PDB) (https://www.rcsb.org/).

Generation of target structures of COVID-19 PL-Pro and Indian Strain Spike

As the structures of COVID-19 PL-Pro and IS-Spike was unavailable in the Protein Data Bank, approaches of *Ab initio* predictions of PL-Pro using I-TASSER **[28]** and Homology modeling was used for predicting the 3D structure of IS-Spike using Swiss model. Templates used for prediction of IS-Spike structure were 6vsb (PDB ID). The quality of the derived structures was further validated by PDBsum server following method described by Yadav *et al.*, 2017 **[29]**. The 3D structures thus generated were visualized by Discovery Studio 3.5.

Energy minimization

All targeted structure whether downloaded from protein data bank or generated from I-TASSER and Swiss model are additionally refined by molecular dynamic programme YASARA (Yet Another Scientific Artificial Reality Application, http://www.yasara.com) **[30].** YASARA server calculates the initial and final energy of COVID-19 protein, which is based on NOVA (Nucleotide Optimization in VAcuo).

Docking analysis

Docking of Ligands with various selected targets was carried out by Hex8.0 and PatchDock Server **[29]** (default parameter RMSD esteem 4.0 and complex type protein-small ligand) trailed by visualization of the docked complexes through Discovery Studio 3.5. Docking investigation was based on geometric shape complementarity score (GSC score), which was determined in PatchDock Server, and binding energy evaluated using Hex8.0. By default parameter like grid dimension (0.6), receptor range (180), ligand range (180), twist range (360) distance range (40), scan step (0.8) was used for the interaction study, assuming ligand is rigid. Docking investigation of Hex depends on spherical polar Fourier (SPF) calculation **[31]**. The findings of the results are based on the docking energy value and the interaction at the binding sites. The more negative value indicates minimum e-value represents more binding affinity hence more steady the complex. In accordance with energy funnel theory less energy depicts very stable conformation. Hence, more energy would be required to break the complex that means elevated dissociation energy. The optimum clusters were selected on the basis of e-value (Binding energy) in Hex 8.0.

Molecular Interaction network

The molecular interaction network of top ten interacting ligands with their selected targets was created in Cytoscape 2.8.3 software **[32].**

Results And Discussion

Ligands preparation and Target selection

In order to carry out the docking analysis, in the beginning the 3D structures of 49 ligands (natural compounds) out of 52 (Table1) were retrieved from PubChem Compound database and three ligands were modeled using ACD/Chem-Sketch.

Many natural compounds reported to have biologically confirmed anti-SARS and anti-MERS coronavirus activity were identified **[33], [34], [16], [17], [18], [19]**. We have selected 21 medicinal plants that have anti-viral property (Table 1 & 4) and their compounds have high probability of directly inhibiting the COVID-19, perhaps providing immediate help in the treatment of the diseases which cause pneumonia.

The prospective targets were selected on the basis of functional categories of molecules: (1) The deubiquitinating enzyme PL-Pro that can reduce host anti-viral response **[12], [13]** (2) 3CLpro or main protease is important to the virus lifecycle **[35]**. (3) Spike binds to the cell membrane protein to enter human cells **[14]**.These three targets provide a great opportunity to identify potential drug candidates for the treatment. COVID-19 3CL-Pro/M-Pro (PDB ID: 6LU7) **[36]** and Spike (PDB ID: 6vsb) **[37]** structures were retrieved from PDB data bank, whereas the structure of PL-Pro and IS-Spike was determined by *Ab-initio* modeling and homology modeling approach as the same was unavailable at PDB data bank. Energy minimization of all targeted 3D structure was done by YASARA server. Initial energy of the Spike, IS-Spike, M-Pro and PL-Pro protein were -135274.6, -378170.5, -126585.8 and 12117262.4 kJ/mol respectively while the end energy of the model is -146567.6, -534242.4,-166967.6 and -848519.5kJ/mol respectively. Energy minimization removes severe steric clashes between two atoms with a distance **[30].** The 3D-Structure of COVID-19 retrieved as well as predicted model was further validated with PDBsum. Ramachandran plot analysis of the Spike, IS-Spike, M-Pro and PL-Pro model showed 83.7%, 86.2%, 91.7% and 74.7% residues come under favored region. The two model which are close to the requisite percentage of 90 for validating model which is near to good model, one cross to 90 i.e. good model, and one below 80 which come under average model. (Fig.2.). Favoured region residues varied between Spike and IS-Spike due to a change of A930V (24351C>T) in IS-Spike COVID-19 (Indian mutant Spike), which revealed that IS-Spike is more stable than general Spike protein. Favoured regions which showed in Ramachandran plot are energetically and sterically stable conformations of residues characterized by values of torsion angles ψ and ϕ. Mutant position in Ramachandran Plot for Predicting Protein Stability of Surface Mutations **[38].**

Docking studies

With the aim of findinga potential candidate for treating COVID-19, molecular docking studies were performed out the virtual screening of 52 ligands. Most of the molecules are active against different viral diseases viz. HIV, Influenza, Herpes, West Nile virus, and Dengue virus. The list of ligands tested for docking study is depicted in Table 1.

Protein-ligand interactions were also decoded with respect to nature of interacting amino acid residues and association of H-bonding. Binding of ligands to the target also indicates to the possibility that the ligand may be capable of ushering functional modulations in the target molecule **[39], [40].** Most of the interacting amino acidic residues along with hydrogen bonding interactions shown by PatchDock analysis and further visualized by Discovery studio 3.5 (Fig.4- 7). The estimation of binding energy evaluation done by Hex8 to provide precious information that can be used to scrutinize the results of approving studies, for instance, *in vitro*, *in vivo* and clinical studies.

All 52 molecules were docked against the target enzyme COVID-19 and ranked based on their dock scores (Binding energy) and were depicted in Table3. In this table, we have mentioned the B.E of each molecule with Spike, IS-Spike, PL-Pro and M-Pro. The column average (avg.) B.E with Spike is avg. of Spike, PL-Pro and M-Pro. Similarly, the column avg. B.E with IS-Spike is avg. of IS-Spike, PL-Pro and M-Pro. Ranking is based on the avg. value of data, in which Rank1 indicates highest avg. binding energy with particular molecule and Rank 2 indicates lesser binding energy as compared to Ranked 1 molecule and so on. We have selected top 10 ligands which have high binding affinity to their targets i.e. Spike, IS-Spike, PL-Pro and M-Pro on the basis of binding energy (calculated by docking) and were depicted in Table2.The 10 leading ligands have high binding affinity for inhibition of Spike protein was Punicafolin (*Phyllanthus emblica*), Emblicanin A (*Phyllanthus emblica*), Lopinavir (Anti-HIV drugs), Punigluconin (*Phyllanthus emblica*), Kuwanon X (*Morus alba*), Rutin (*Azadirachta indica*), Phyllanemblinin A (*Phyllanthus emblica*), Lithospermic Acid (*Salvia miltiorrhiza*), Amaroswerin

(*Swertia chirata*) and Heptacosanol (*Eclipta prostrata*).The standard drugs like Lopinavir, Hydroxychloroquinine and Ribavirin, which interact with Spike plus it come under 3, 15 and 21 rank out of 52. First 10 ligands have high binding affinity for inhibition of IS-Spike protein was Punigluconin (*Phyllanthus emblica*), Emblicanin A (*Phyllanthus emblica*), Rutin (*Azadirachta indica*), Lopinavir (Anti HIV drugs), Punicafolin (*Phyllanthus emblica*), Amarogentin (*Swertia chirata*), Azadirachtin (*Azadirachta indica*), Amaroswerin (Anti HIV drugs), Phyllanemblinin A (*Phyllanthus emblica*) and Lithospermic Acid (*Salvia miltiorrhiza*). The standard drugs such as Lopinavir, Hydroxychloroquinine and Ribavirin, which interact with Spike as well as they ranked on 4, 20 and 41. The 10 major ligands have high binding affinity for inhibition of PL-Pro protein was Punicafolin (*Phyllanthus emblica*), Emblicanin A (*Phyllanthus emblica*), Punigluconin (*Phyllanthus emblica*), Lopinavir (*Anti HIV drugs*), Phyllanemblinin A (*Phyllanthus emblica*), Amarogentin (*Swertia chirata*), Lithospermic Acid (*Salvia miltiorrhiza*), Azadirachtin (*Azadirachta indica*), Rutin (*Azadirachta indica*) and Amaroswerin (*Swertia chirata*). The standard drugs viz. Lopinavir, Hydroxychloroquinine and Ribavirin, which interact with PL-Pro and they ranked on 4, 20 and 41. The top 10 ligands have high binding affinity for inhibition of M-Pro protein was Punicafolin (*Phyllanthus emblica*), Emblicanin A (*Phyllanthus emblica*), Punigluconin (*Phyllanthus emblica*), Lopinavir (Anti HIV drugs), Kuwanon x (*Morus alba*), Rutin (*Azadirachta indica*), Lithospermic Acid (*Salvia miltiorrhiza*), Amaroswerin (*Swertia chirata*), Phyllanemblinin A (*Phyllanthus emblica*) and Amarogentin (*Swertia chirata*).The standard drugs i.e. Lopinavir, Hydroxychloroquinine and Ribavirin, which interact with M-Pro and it fall under rank 4, 24 and 43. The binding affinity of ligands with M-Pro and PL-Pro is better than Spike and IS-Spike so M-Pro and PL-Pro is better inhibitory target protein for inhibitory drugs. After comparative analysis of Spike and IS-Spike, we conclude that binding affinity of ligands with IS-Spike get low as compared to Spike so inhibitory potential of drugs may fragile (Table2 and 3).

Based on the avg. B.E with Spike, PL-Pro and M-Pro (Table3), we preferred best 10 ligands {Punicafolin (*Phyllanthus emblica*), Emblicanin A (*Phyllanthus emblica*), Punigluconin (*Phyllanthus emblica*), Lopinavir (Anti HIV drugs), Kuwanon X (*Morus alba*), Rutin (*Azadirachta indica*), Lithospermic Acid (*Salvia miltiorrhiza*), Phyllanemblinin A (*Phyllanthus emblica*), Amarogentin (*Swertia chirata*) and Amaroswerin (*Swertia chirata*)} for inhibition of all three targets (Spike, PL-Pro and M-Pro). On the basis of avg. B.E of IS-Spike, PL-Pro and M-Pro (Table3.), we favoured best 10 ligands {Punicafolin (*Phyllanthus emblica*), Emblicanin A (*Phyllanthus emblica*), Punigluconin (*Phyllanthus emblica*), Lopinavir (Anti HIV drugs) Rutin (*Azadirachta indica*), Amarogentin (*Swertia chirata*) and Amaroswerin (*Swertia chirata*), Phyllanemblinin A (*Phyllanthus emblica*), Lithospermic Acid (*Salvia miltiorrhiza*) and Kuwanon x (*Morus alba*) for inhibition of three targets (IS-Spike, PL-Pro and M-Pro). Based on the avg. B.E of Spike, PL-Pro and M-Pro as well as IS-Spike, PL-Pro and M-Pro, the standard drugs Lopinavir come under 4^{th} rank, Hydroxychloroquine on 23^{rd} rank and Ribavirin on 40^{th} rank, out of 52 ligands.

In Table4, 49 compounds have been taken from 21 different medicinal plants and rests of three were standard drugs. Avg. value is calculated on the basis of each medicinal plant's compound i.e.

$$\text{Average value} = \frac{\text{Sum of Binding Energy of each compound taken from "X"}}{\text{Total no. of compound taken from "X"}}$$

"X" denotes Medicinal Plant

We have ranked 21medicinal plants (possess 49 ligands) along with standard drugs (3 drugs) (Table4.) based on Avg. B.E (KJ/mol) with Spike, PL-Pro and M-Pro, and similarly ranked 21 medicinal plants (possess 49 ligands) along with standard drugs (3 drugs) (Table4) on the basis of Avg. B.E (KJ/mol) with Indian strain Spike, PL-Pro and M-Pro. From table 4 it is very clear that Malberry (*Morus alba*) is the most effective plant as compared to the other plants and standard drugs. While Amla (*Phyllanthus emblica*) is the second most effective medicinal plant. But in case of IS-Spike Amla (*Phyllanthus emblica*) is the most effective medicinal plant when compared with others.

There are four ligands out of top 10 whichare common in all four different networks and those come from *Phyllanthus emblica* (Amla) plus minimum one compound (Rutin) of *Azadirachta indica* (Neem) out of 4 and a compound (

Amaroswerin) of *Swertia chirata*, which is common in all networks. Moreover, a standard drug Lopinavir and a compound (Lithospermic Acid) of *Salvia miltiorrhiza* are common in all networks. Therefore, it looks logical that the compounds which are common in the entire network should have more inhibitory potential against COVID19 due to the better binding potential among all three target proteins including IS-Spike as displayed in Fig.3.

Table2. Comparative analysis of top 10 selected valuable ligands interacted with COVID-19 Spike, Indian mutant Spike, PL-Pro and M-Pro.

Top ran king	Molecular name	GCC Spike	B.E (KJ/mol) of Spike	Molecular name	GCC India n mut Spike	B.E (KJ/mol) of Indian mutant	Molecular name	GCC PL-Pro	B.E (KJ/mol) of PL-Pro	Molecular name	GCC M-Pro	B.E (KJ/mol) of M-Pro
1	Punicafolin	6628	-293.66	Punigluconin	6736	-249.01	Punicafolin	7990	-452.28	Punicafolin	6878	-492.34
2	Emblicanin A	6336	-292.51	Emblicanin A	6794	-247.92	Emblicanin A	7056	-446.87	Emblicanin A	6380	-458
3	Lopinavir	7258	-280.47	Rutin	6354	-240.45	Punigluconin	7452	-434.4	Punigluconin	6492	-456.87
4	Punigluconin	6654	-274.05	Lopinavir	7524	-232.54	Lopinavir	8902	-394.06	Lopinavir	7070	-425.97
5	Kuwanon x	6256	-258	Punicafolin	7130	-229.36	Phyllanemblinin A	6826	-385.38	Kuwanon x	5768	-405.1
6	Rutin	6216	-242.48	Amarogentin	6356	-229.13	Amarogentin	7126	-383.64	Rutin	6156	-384.76
7	Phyllanemblinin A	6050	-234.85	Azadirachtin	6558	-225.95	Lithospermic Acid	6854	-383.13	Lithospermic Acid	5792	-373.81
8	Lithospermic Acid	5862	-233	Amaroswerin	6274	-223.9	Azadirachtin	6928	-377.57	Amaroswerin	5894	-368.89
9	Amaroswerin	6036	-230.98	Phyllanemblinin A	6072	-204.88	Rutin	7056	-367.75	Phyllanemblinin A	5744	-367.1
10	Heptacosanol	6270	-228.92	Lithospermic Acid	6104	-200.21	Amaroswerin	6858	-365.55	Amarogentin	5808	-365.34

Table3. Comparative docking study results on COVID-19 enzymes.

Sl.No.	Molecular name	Source/Std drugs	Common Name	B.E (KJ/mol) of IS- Spike - Ligands	B.E (KJ/mol) of Spike- Ligands	B.E (KJ/mol) of PL- Pro- Ligands	B.E (KJ/mol) of M- Pro- Ligands	Avg. B.E (KJ/mol) with Spike	Rank	Avg. B.E(KJ/mol)with IS- Spike	Rank
1	Punicafolin	*Phyllanthus emblica*	Amla	-229.36	-293.66	-452.28	-492.34	-412.76	1	-391.33	1
2	Emblicanin A	*Phyllanthus emblica*	Amla	-247.92	-292.51	-446.87	-458	-399.13	2	-384.26	2
3	Punigluconin	*Phyllanthus emblica*	Amla	-249.01	-274.05	-434.4	-456.87	-388.44	3	-380.09	3
4	Lopinavir	*Anti HIV drugs*	Anti HIV drugs	-232.54	-280.47	-394.06	-425.97	-366.83	4	-350.86	4
5	Kuwanon x	*Morus alba*	Mulberry	-192.23	-258	-358.03	-405.1	-340.38	5	-318.45	10
6	Rutin	*Azadirachta indica*	Neem	-240.45	-242.48	-367.75	-384.76	-331.66	6	-330.99	5
7	Lithospermic Acid	*Salvia miltiorrhiza*	Red sage	-200.21	-233	-383.13	-373.81	-329.98	7	-319.05	9
8	Phyllanemblinin A	*Phyllanthus emblica*	Amla	-204.88	-234.85	-385.38	-367.1	-329.11	8	-319.12	8
9	Amarogentin	*Swertia chirata*	Chirayta	-229.13	-221.5	-383.64	-365.34	-323.49	9	-326.04	6
10	Amaroswerin	*Swertia chirata*	Chirayta	-223.9	-230.98	-365.55	-368.89	-321.81	10	-319.45	7
11	Azadirachtin	*Azadirachta indica*	Neem	-225.95	-224.46	-377.57	-342.81	-314.95	11	-315.44	11
12	Isoquercitrin	*Houttuynia cordata*	Fish mint	-186.09	-205.32	-326.61	-315.76	-282.56	12	-276.15	13
13	Hentriacontanol	*Eclipta prostrata*	Bhringraj	-169.78	-217.03	-284.14	-344.52	-281.90	13	-266.15	18
14	Nimbaflavone	*Azadirachta indica*	Neem	-199.83	-212	-321.59	-311.62	-281.74	14	-277.68	12
15	Heptacosanol	*Eclipta prostrata*	Bhringraj	-170.01	-228.92	-284.14	-326.21	-279.76	15	-260.12	21
16	Hyperoside	*Azadirachta indica*	Neem	-188.14	-192.9	-328.47	-309	-276.79	16	-275.20	14
17	Thalimonine	*Thalictrum simplex L.*	Meadow rue	-141.45	-225.37	-298.63	-304.7	-276.23	17	-248.26	24

18	Baicalin	*Scutellaria baicalensis*	Baikal skullcap	-192.07	-195.01	-325.29	-304.64	-274.98	18	-274.00	16
19	Stigmasterol	*Eclipta prostrata*	Bhringraj	-184.59	-184.29	-333.34	-301.94	-273.19	19	-273.29	17
20	Quercitrin	*Houttuynia cordata*	Fish mint	-184.69	-170.57	-340.69	-296.85	-269.37	20	-274.08	15
21	Betulinic acid	*Symplocos racemosa*	Lodhra	-152.89	-191.59	-318.5	-295.43	-268.51	21	-255.61	22
22	Curcumin	*Curcuma longa*	Turmeric	-182.11	-193.64	-290.36	-316	-266.67	22	-262.82	19
23	Hydroxychloroquine	Anti Malarian drug	Anti Malarian drug	-174.59	-212.31	-302.02	-284.17	-266.17	23	-253.59	23
24	Mangiferin	*Swertia chirata*	Chirayta	-186.26	-179.78	-306.83	-287.63	-258.08	24	-260.24	20
25	Calanolide A	*Calophyllum Spp*	Indian doomba oil tree	-153.69	-192.85	-292.69	-281.06	-255.53	25	-242.48	27
26	Gentiopicrin	*Swertia chirata*	Chirayta	-146.31	-207.26	-275.75	-269.6	-250.87	26	-230.55	34
27	Flavonoid	*Phyllanthus emblica*	Amla	-157.89	-181.39	-301.3	-269.49	-250.73	27	-242.89	25
28	Tinosoprin A	*Tinospora cordifolia*	Giloy	-133.77	-162.75	-289.3	-279.49	-243.85	28	-234.19	29
29	Sweroside	*Swertia chirata*	Chirayta	-138.76	-171.44	-273.27	-280.21	-241.64	29	-230.75	33
30	Piperine	*Piper longum*	Indian long pepper	-142.25	-170.94	-273.36	-277.91	-240.74	30	-231.17	32
31	Piper longumine	*Piper longum*	Indian long pepper	-158.25	-149.86	-285.96	-283.55	-239.79	31	-242.59	26
32	Swertiamarin	*Swertia chirata*	Chirayta	-150.87	-168.53	-274.78	-273.88	-239.06	32	-233.18	30
33	Quercitin	*Houttuynia cordata*	Fish mint	-128.81	-211.98	-245.18	-259.05	-238.74	33	-211.01	37
34	Kaempferol	*Phyllanthus emblica*	Amla	-129.74	-205.25	-248.38	-251.81	-235.15	34	-209.98	38
35	Palmatine	*Tinospora cordifolia*	Giloy	-151.54	-157.84	-279.53	-265.39	-234.25	35	-232.15	31
36	Jatorrohizine	*Tinospora cordifolia*	Giloy	-166.22	-156.13	-281.01	-263.65	-233.60	36	-236.96	28
37	Berberine	*Tinospora cordifolia*	Giloy	-138.6	-146.84	-271.59	-278.24	-232.22	37	-229.48	36
38	Magnoflorine	*Tinospora cordifolia*	Giloy	-156.05	-160.59	-272.87	-260.3	-231.25	38	-229.74	35
39	Resveratrol	*Veratrum grandiflorum*	Corn lilies	-117.42	-184.25	-250.46	-237.71	-224.14	39	-201.86	39
40	Ribavirin	Anti HIV drugs	Anti HIV drugs	-114.61	-195.18	-227.72	-211.73	-211.54	40	-184.69	40
41	Zingerone	*Zingiber officinale*	Ginger	-100.47	-185	-235.15	-207.5	-209.22	41	-181.04	43
42	DesmethylWeddolactone	*Eclipta prostrata*	Bhringraj	-96.6	-185.82	-208.98	-208.54	-201.11	42	-171.37	45
43	Weddolactone	*Eclipta prostrata*	Bhringraj	-105.33	-174.16	-205.3	-213.9	-197.79	43	-174.84	44
44	Ajoene	*Allium sativum L.*	Garlic	-105.18	-149.54	-209.93	-232.46	-197.31	44	-182.52	41
45	Harmine	*Peganum harmala*	Wild rue	-115.55	-151.01	-208.06	-220.17	-193.08	45	-181.26	42
46	Bicyclogermacrene	*Glechon marifolia*	Mint	-109.44	-159.85	-190.79	-201.21	-183.95	46	-167.15	46
47	Eugenol	*Eugenia caryophyllus*	Clove	-86.04	-153.97	-206.73	-180.5	-180.40	47	-157.76	47
48	S-Allyl-L-cysteine	*Allium sativum L*	Garlic	-80.79	-170.4	-183.93	-177.61	-177.31	48	-147.44	49
49	Diallyltrisulfide (DTS)	*Allium sativum L.*	Garlic	-74.79	-136.08	-182.24	-189.51	-169.28	49	-148.85	48
50	Allicin	*Allium sativum L.*	Garlic	-80.28	-148.56	-166.1	-190.38	-168.35	50	-145.59	50
51	Homonojirimycin	*Omphalea diandra*	Omphalea diandra	-80.02	-155.81	-169.44	-174.27	-166.51	51	-141.24	51
52	Diallyl disulfide(DDS)	*Allium sativum L.*	Garlic	-75.21	-126.93	-161.81	-181.93	-156.89	52	-139.65	52

Table4. Comparative analysis of 21 medicinal plants along with standard drugs screened for effective medicinal plants as compared to standard drugs.

Common Name	Pharmacological function	References	total compoun d for this study	Avg. B.E (KJ/mol) with Spike	Rank	Avg. B.E (KJ/mol) with IS- Spike	Rank
Mulberry	Anti-viral	([41]	1	-340.38	1	-318.45	3
Amla	Anti-viral, Antiyretic, Analgesic, Antitussive, Antiatherogeric	[42]	6	-335.89	2	-321.28	1
Red sage	Anti-viral	[43]	1	-329.98	3	-319.05	2
Neem	Anti-viral	[44]	4	-301.28	4	-299.83	4
Anti HIV drugs	Anti-viral	[45]	2	-289.19	5	-267.77	6
Meadow rue	Anti-Influenza	[46]	1	-276.23	6	-248.26	12
Baikal skullcap	Anti-viral	[47]	1	-274.98	7	-274.00	5
Chirayta	Anti-viral, Antifungal, Antiinflamatory & Anticancer	[48]	6	-272.49	8	-266.70	7
Lodhra	Anti-viral	[49]	1	-268.51	9	-255.61	9
Turmeric	Anti-viral	[50]	1	-266.67	10	-262.82	8
Anti Malarian drug	Anti-viral	[51]	1	-266.17	11	-253.59	11
Fish mint	Anti-viral & Immuno stimulant	[52]	3	-263.56	12	-253.75	10
Indian doomba oil tree	Anti-HIV	[53]	1	-255.53	13	-242.48	13
Bhringraj	Anti-viral, Anti-oxidant, Antianalgesic & Antibacterial	[54]	5	-246.75	14	-229.15	16
Indian long pepper	Anti-viral	[34]	2	-240.26	15	-236.88	14
Giloy	Anti-HIV, Antipyretic,Anti-inflammatory	[55]	5	-235.03	16	-232.50	15
Corn lilies	Anti-viral	[56]	1	-224.14	17	-201.86	17
Ginger	Anti-viral	[57]	1	-209.22	18	-181.04	19
Wild rue	Anti-viral	[58]	1	-193.08	19	-181.26	18
Mint	Anti-viral & Antifungal	[59]	1	-183.95	20	-167.15	20
Clove	Anti-viral, Antifungal & Antibacterial	[60]	1	-180.40	21	-157.76	21
Garlic	Antiviral, Antimicrobial, Reduce risk of cardiovascular diseases	[61]	5	-173.83	22	-152.81	22
Omphalea diandra	Anti-viral	[62]	1	-166.51	23	-141.24	23

Conclusion

At present, COVID-19 has spreads in the entire worldwhichwas initially appeared in China (Wuhan). There is no approved medicine or vaccine presently exists to treat this disease. The main purpose of present investigation was scrutinizing several medicinal plant derived compounds that may be used to inhibit the COVID-19 contagious disease. Bioinformatics approaches can be used for rapid detection method for potential therapeutics for drug discovery. We have identified 10 leading ligands by virtual screening of 52 ligands, which have high binding affinity to their targets i.e. Spike, Indian strain Spike, PL-Pro and M-Pro on the basis of binding energy.

Based on the calculation of avg. B.E with Spike, PL-Pro and M-Pro (Table3.), we determined best 10 ligands were Punicafolin, Emblicanin A, Punigluconin, Lopinavir, Kuwanon X, Rutin, Lithospermic Acid, Phyllanemblinin A, Amarogentin and Amaroswerin for inhibition of all three targets (Spike, PL-Pro and M-Pro). Similarly, on the basis of avg. B.E of Indian strain Spike, PL- Pro and M-Pro, we identified first 10 ligands viz. Punicafolin, Emblicanin A, Punigluconin, Lopinavir, Rutin, Amarogentin, Amaroswerin, Phyllanemblinin A, Lithospermic Acid and Kuwanon X for inhibition of three targets (Indian strain Spike, PL-Pro and M-Pro).These drugs may act as potential inhibitors against COVID-19 tri-targets.

We have sorted 21medicinal plants (have 49 ligands) along with standard drugs (3 drugs) based on avg. B.E (KJ/mol) with Spike, PL-Pro and M-Pro, and similarly ranked 21 medicinal plants along with standard drugs on the basis of Avg. B.E

(KJ/mol) with Indian strain Spike, PL-Pro and M-Pro and conclude that Mulberry (*Morus alba*) is the most effective plant as compared to the other medicinal plants and standard drugs. Although Amla (*Phyllanthus emblica*) is the second most effective medicinal plant. However, in case of IS-Spike Amla (*Phyllanthus emblica*) is the most effective medicinal plant when compared with others. The predicted binding and ordering of drugs should also be useful to deduce the results of existing clinical trials that are verifying small molecule drugs for efficacy against COVID-19.

Declarations

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Conflict of interest: None

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Tables

Due to technical limitations, Table 1 is only available as a download in the supplemental files section

Figures

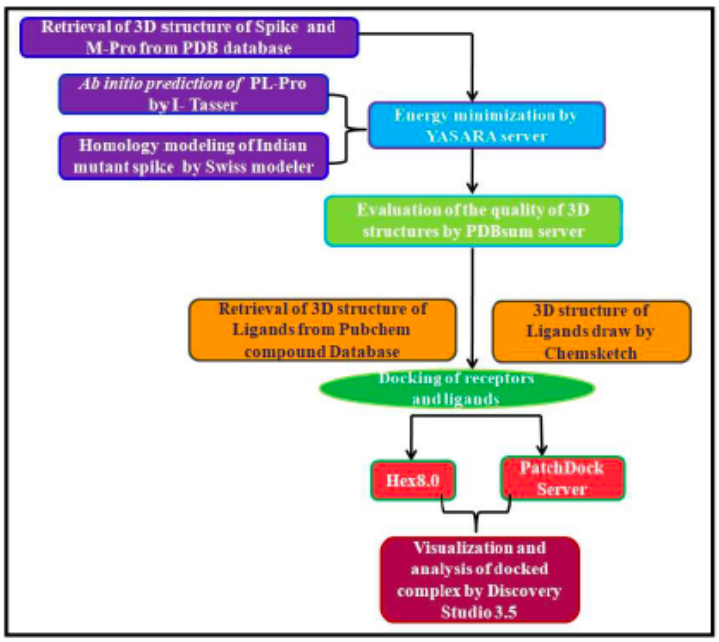
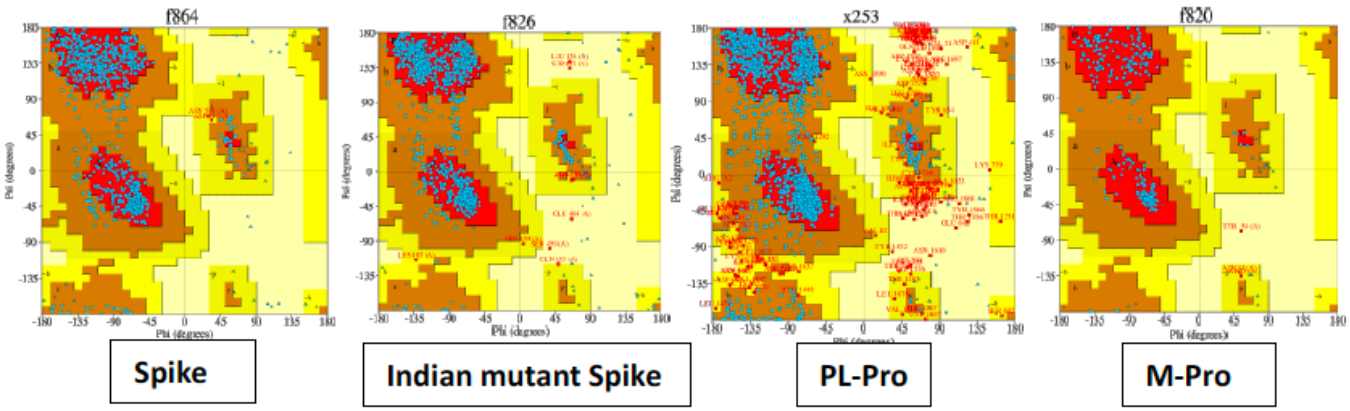


Figure 1

Experimental flow chart



COVID-19 protein	Most favoured regions [A,B,L]	Additional allowed regions [a,b,l,p]	Generously allowed regions [~a,~b,~l,~p]	Disallowed regions [XX]
Spike	83.7%	16.0%	0.2%	0.0%
IS-Spike	86.2%	12.8%	0.4%	0.5%
PL-Pro	74.7%	19%	3.8%	2.5%
M-Pro	91.7%	7.2%	0.8%	0.4%

Figure 2

Quality validation of 3D structure of Target proteins by PDB Sum

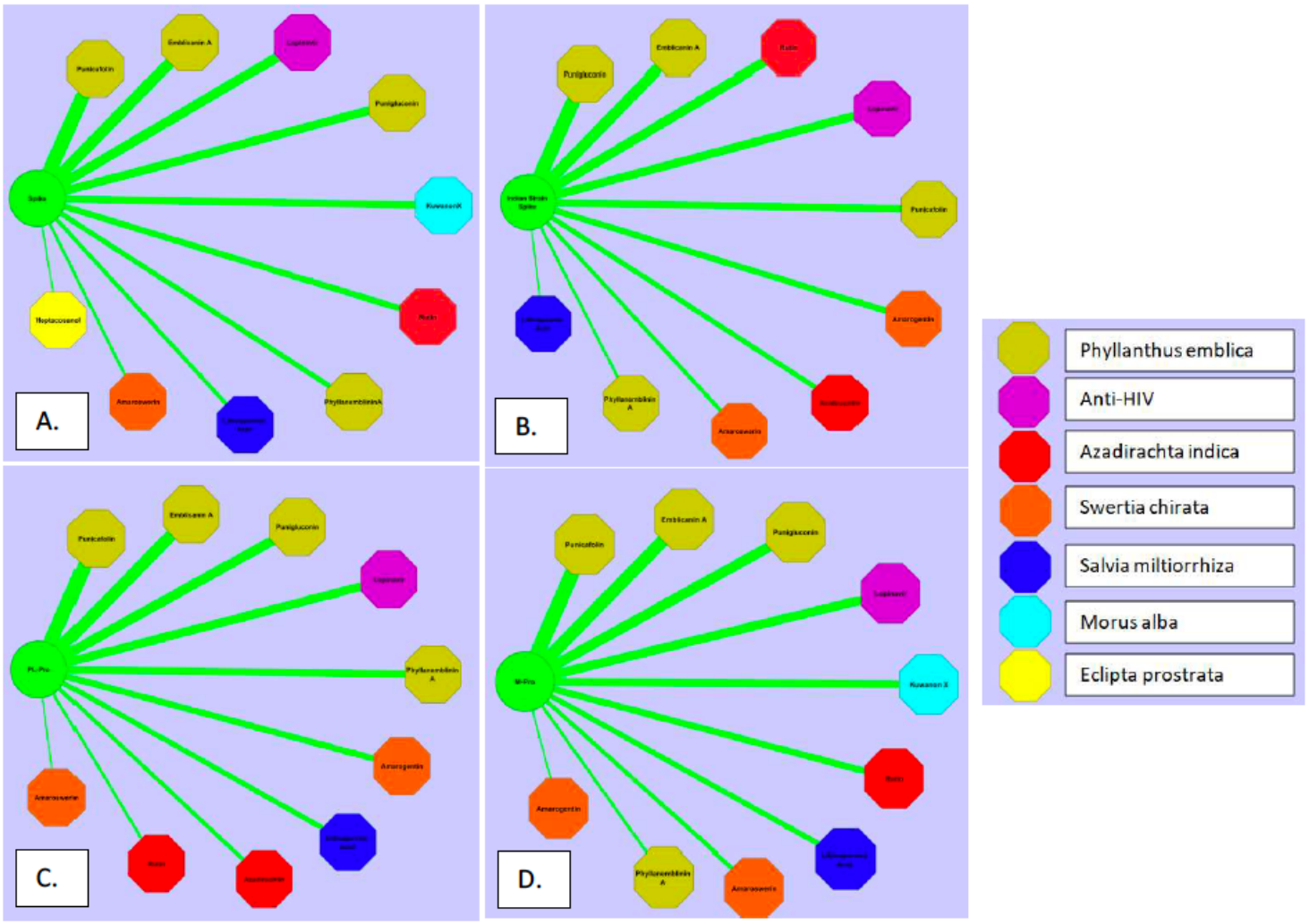


Figure 3

Network analysis of top 10 selected ligands interaction with their target proteins of COVID-19. Here green color oval shaped nodes indicate the target proteins of COVID-19 such as (A.) Spike, (B.) IS-Spike, (C.) PL-Pro and (D.) M-Pro/3CL-Pro. The octagonal shape like nodes represent ligands and their diverse color indicates different medicinal plants and a standard drug. The edge between the two nodes indicates protein-ligands interaction and has higher thickness of edge showed high binding affinity between them and vice-versa.

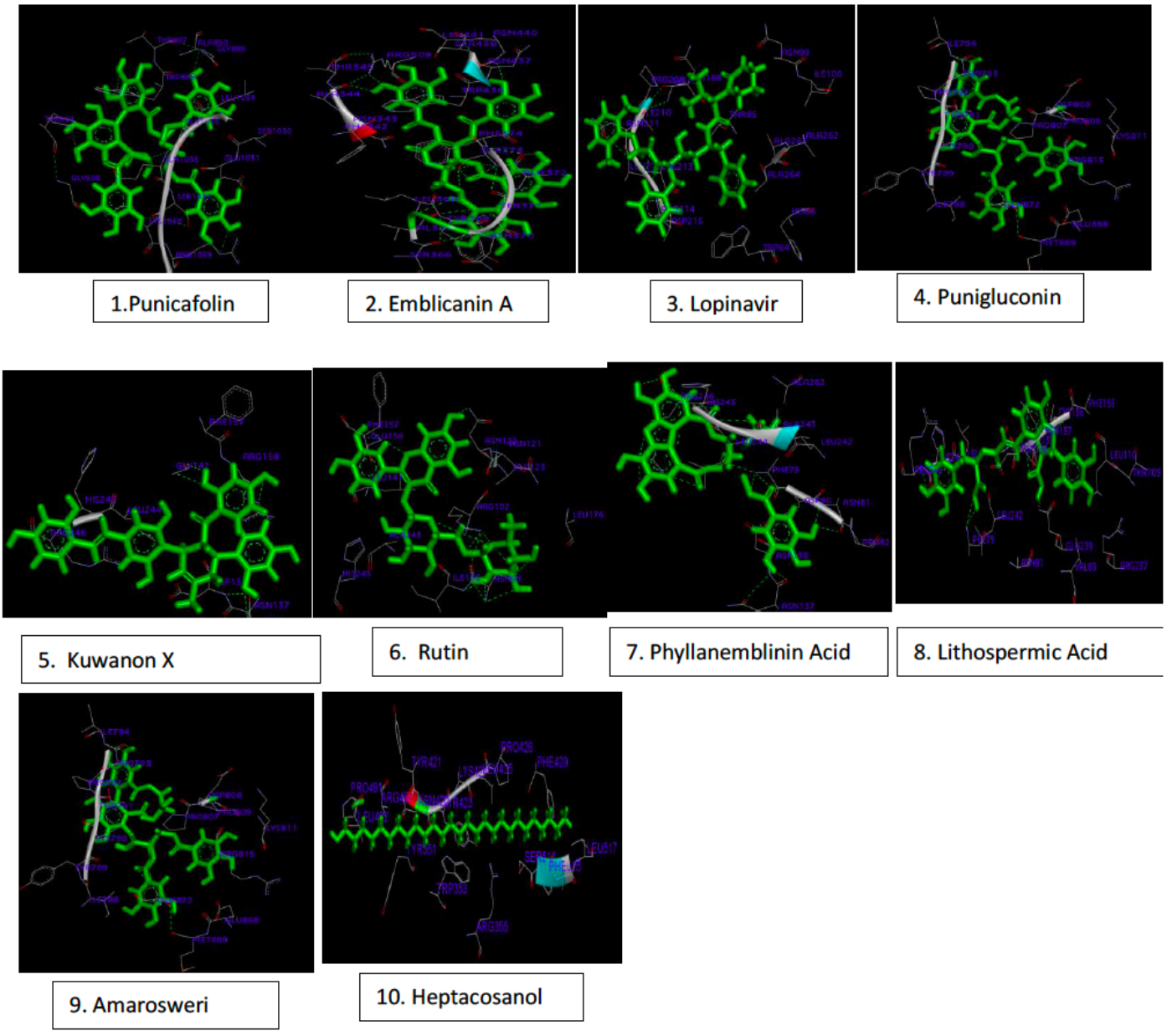


Figure 4

Experimentally determined 3D plot of top 10 leading Spike-ligands interaction. Green colour dash indicates H-bond interaction between atoms.

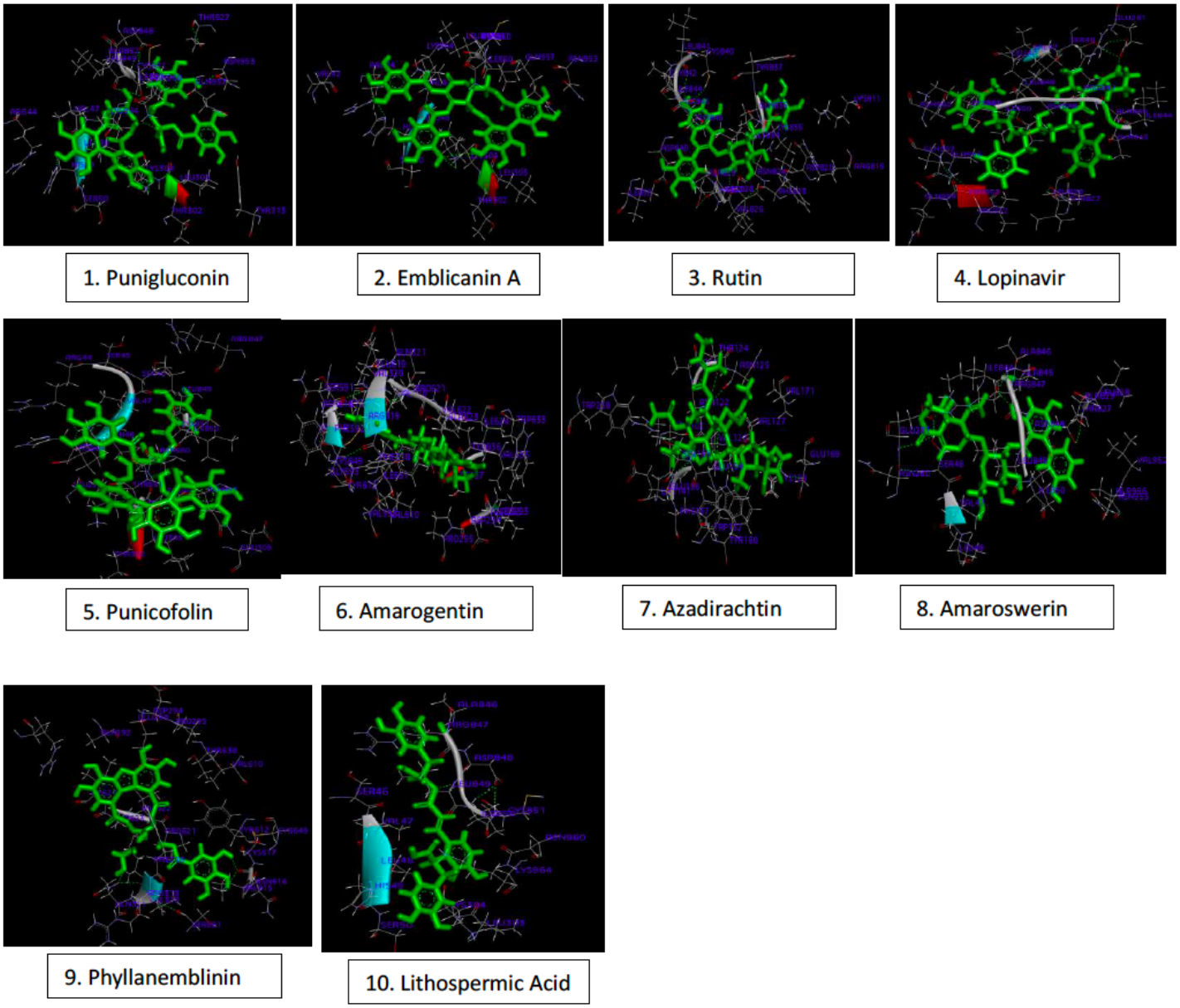


Figure 5

Experimentally determined 3D plot of top 10 Indian strain Spike-ligands interaction. Green colour dash indicates H-bond interaction between atoms.

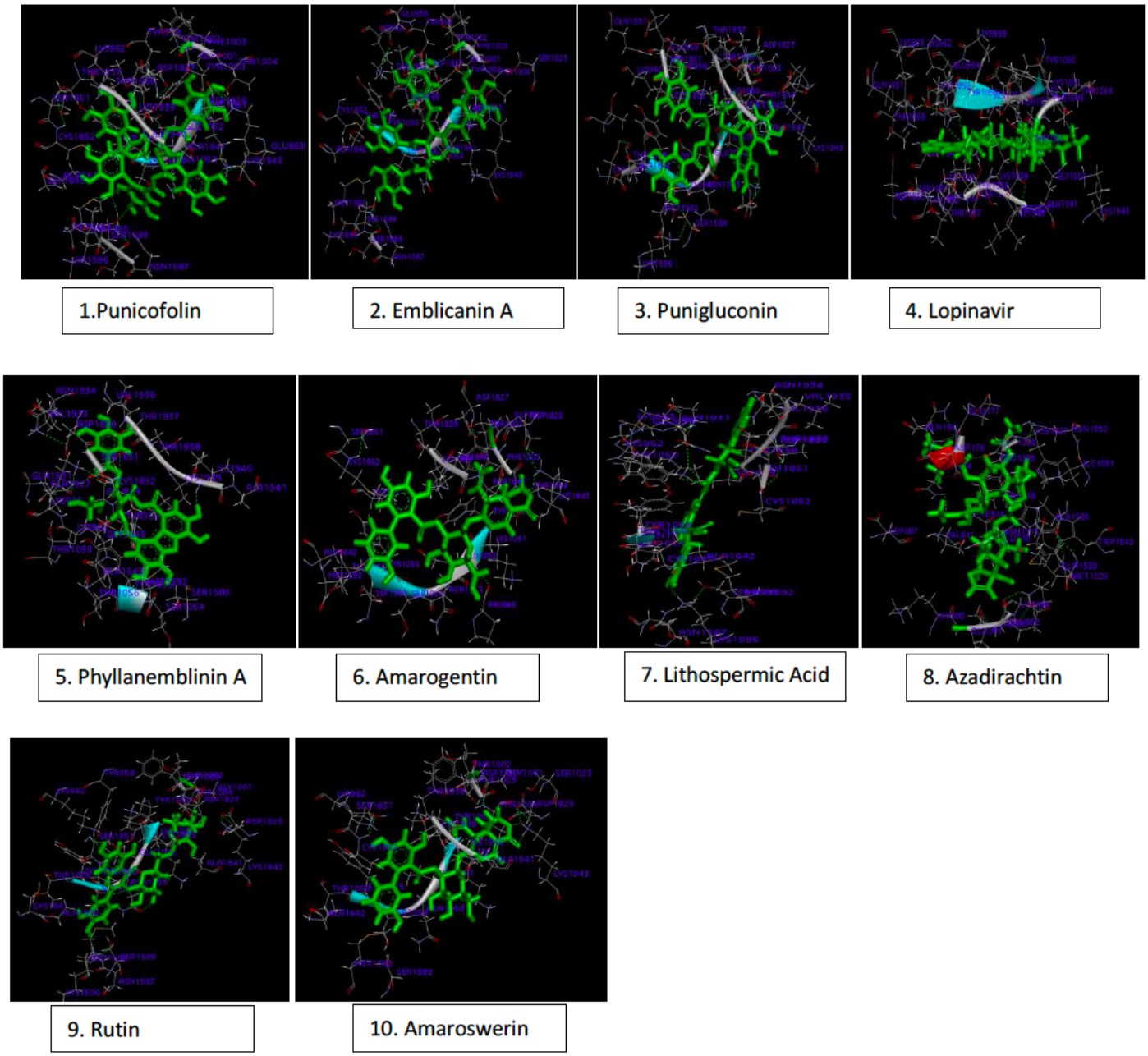


Figure 6

Experimentally determined 3D plot of first 10 PL-Pro -ligands interaction. Green colour dash indicates H-bond interaction between atoms.

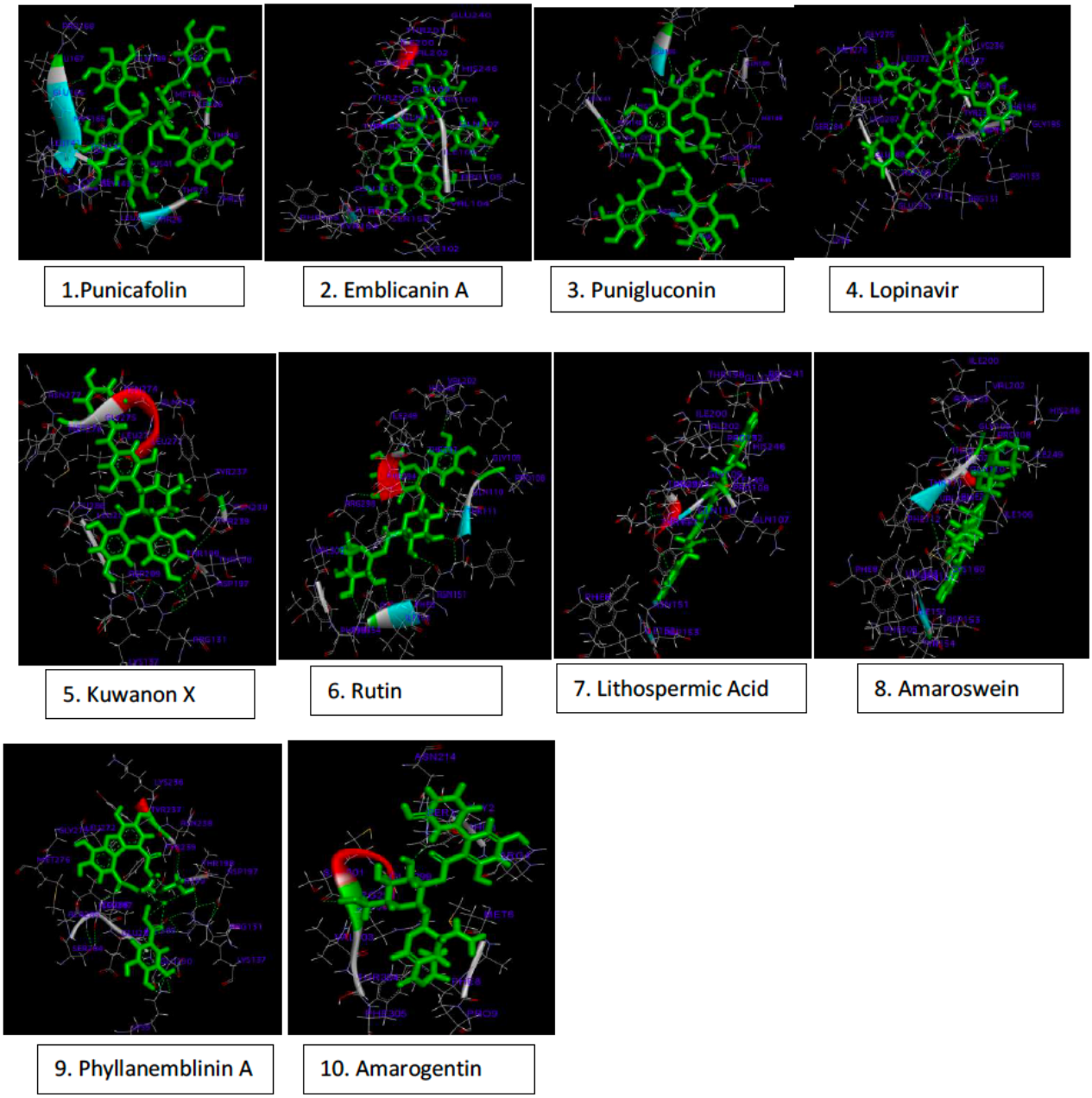


Figure 7

Experimentally determined 3D plot of ten main M-Pro-ligands interaction. Green colour dash indicates H-bond interaction between atoms.

Supplementary Files

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- Table1.docx