Original Article

In-silico Strategies of Some Selected Phytoconstituents from *Zingiber officinale* as SARS CoV-2 Main Protease (COVID-19) Inhibitors

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ABSTRACT

Background: *Zingiber officinale* (Zingiberaceae) has been utilized to remedy many afflictions of humans. Literary works illustrate that it possesses numerous biological activities. **Methods:** Today, research study intended to recognize the Phyto-derived anti-viral substances from *Zingiber officinale* against COVID-19 main protease enzyme and to understand the molecular basis of its activity. Methods: In the present study, 42 molecules obtained from *Z. officinale*, which are retrieved from the Pubmed database, are studied via docking study. Docking study was performed using Autodock vina and PyRx software. Afterwards, admet SAR, as well as Dru Li to servers, were made use of for drug-likeness prophecy. **Results:** Our study shows that the nine phytochemicals of *Z. officinale* are very likely against the main protease enzyme of COVID-19. Utilizing contemporary strategies, these phyto-compounds might use to establish a reliable medication from a natural origin. **Conclusion:** The substances identified potential as possible anti-virals. However, even more, *in-vitro* studies are needed to examine their effectiveness versus COVID-19.

Key words: *Zingiber officinale*, ADMET, PyRx, Physico-chemical, PASS analysis.

INTRODUCTION

WHO has currently stated a typical emergency situation and also pandemic for the coronavirus (COVID-19) that has proactively propagating around the entire world. The virus SARS-CoV-2 can easily trigger signs and symptoms such as high temperature, coughing, pneumonia, queasiness, as well as exhaustion.[1] The epidemiological history of the infection was actually believed to derive from a seafood market in Wuhan, China. Having said that, the exact origin of the preliminary transmission to human beings is actually still unidentified. Presently, there is actually > 100 total genome patterns recognized in the NCBI GenBank, coming from over ten nations. The variant in between these series is actually much less than 1%.The SARS-CoV-2 has been identified as β-coronavirus causes severe respiratory tract infection in humans and utilize angiotensin-converting enzyme 2 (ACE2) receptors to infect humans.[3] Chinese experts separated SARS-CoV-2 and also sequenced the genome SARS-CoV2 on January 7, 2020.[4] The crystallized kind of COVID-19 primary protease (M_{pro}) was actually displayed through a Chinese scientist Liu et cetera (2020) that it is actually a possible medication aim at target protein for the inhibition of

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SARS-CoV-2 replication. The M_{pro} is an essential protein required for the proteolytic maturation of the virus.[5] Thus, targeting M_{pro} has the potential to provide effective treatment against SARS-CoV-2 by inhibition of the viral polypeptide cleavage. The spike protein of virus binds to the tissues membrane layer with a receptor-mediated communication which enables a way to the host cell and also this makes it possible for the application of the well-known protein designs to rapidly develop a version for medicine break through on this brand-new SARS-CoV-2.[6] While standard procedures of medicine finding might take years, the strategy taken right here to look for available medicines for the SARS-COV-2 resides *in silico* docking styles coming from proteins in the SARS-CoV-2, the spike glycoprotein, as well as the SARS-CoV-2 main protease. *In-silico* based testing has confirmed to be a handy tool t to satisfy the obstacles of anti-viral medication invention. Variety of natural or synthetic substance collections through computational assessment strategies as docking conserves information in terms of money as well as time.[7] Natural compounds have served humans as cheaper and safer drug candidates against several diseases and historically been beneficial to human health since the dawn of medicine.[8-10] Thus, we have screened a small library of natural compounds against M_{pro} by *in silico* based screening. In the present research, we have chosen ginger, which is a potent source of anti-viral agents.[11-13] *Zingiber officinale* (Zingiberaceae) is a traditional Indian medicine used for hundreds of year to relieve various lung-related disorders includes pneumonia, infectious disease, as well as malignant pleural effusion.[14,15] Recently, several studies also provided scientific data to support and unveil its antioxidant, antimicrobial, anti-diabetic, anticancer, anti-inflammatory, analgesic, antipyretic, immune-modulator, anti-obesity, hepato-protective, anti-angiogenic, larvicidal, anthelmintic, neuroprotective, gastroprotective and cardiovascular activity.

MATERIALS AND METHODS

Data Source

A list of active phytochemicals was acquired from Indian Medicinal Plants, Phytochemistry and Therapeutic Data Base.[16,17]

Docking Studies

Preparation of Protein

The protein's atomic coordinates, COVID-19 (PDB ID: 6LU7), were retrieved from the RCSB PDB site. The charge assignment, solvation parameters and fragmental volumes to the protein were performed using Autodock Tool 4 (ADT) before study or docking. The protein molecule was further designed for molecular docking[18] (Figure 1).

Preparation of ligands and analysis of drug likeliness

The crystal 3D structure of 42 active compounds from ginger including Aframodial (PubChem CID-9905088), [6]-Paradol (PubChem CID- 94378), [6]-Shogaol (PubChem CID- 5281794), beta-Cadinene (PubChem CID-10657), Cedr-8-ene (PubChem CID- 6431015), Copaene (PubChem CID- 12303902), Gingerenone-A (PubChem CID- 5281775), Isogingerenone B (PubChem CID- 5318568), Shogasulfonic acid A (PubChem CID-10388428) and Zonarene (PubChem CID- 6428488) were retrieved from PubChem dabase.[19] Drug-likeliness properties of ligands were analyzed for the selected active compounds using DruLiTo software[20] (Figure 2).

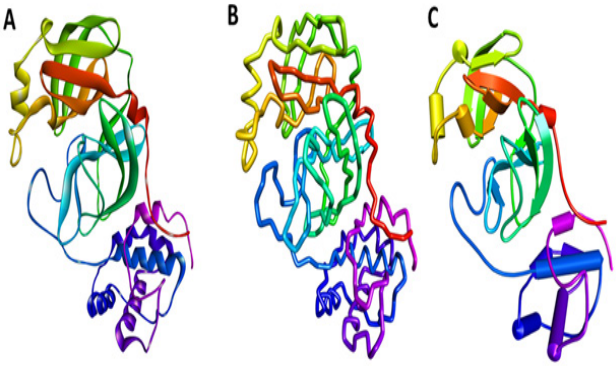

Figure 1: Three Dimensional Crystal Structure of the molecular target, COVID-19 main protease (6LU7) was represented in (A) Solid ribbon (B) Tube (C) Schematic.

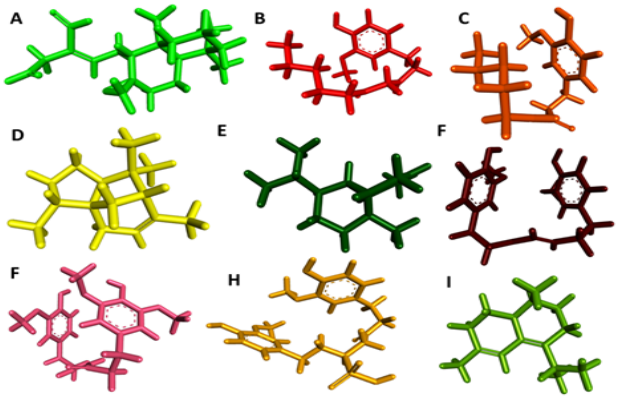

Figure 2: The Three Dimensional structures of ligands. (A) Aframodial (B) [6]-Paradol (C) [6]-Shogaol (D) Cedr-8-ene (E) Copaene (F) Gingerenone-A (G) Isogingerenone-B (H) Shogasulfonic acid A (I) Zonarene.

Compound screening using PyRx program

The auto-dock wizard was used as docking engine to molecular check all compound libraries with PyRxoftware.[21] The ligands were found versatile during the do process, and and the protein should be rigid. The grid parameter configuration file was created with PyRx Auto Grid motor. In the test, the amino acids in the active protein site reacting with the nds have werebeen known/prd. The tests tests e root-middlemean-square deviation (RMSD) of less than 1.0Å were deemed optimal and grouped together to determine the desirable relation. The lowest (most negative) binding energy was recognized as the most binding ligand.

Analysis and visualization

Visual examination of the docking site was performed using Biovia Drug discoverdio 2019, and and the results were validated using AodockVina.[22]

ADMET Analysis

ADMET of the ligands is their pharmacokinetic properties that are required to be examined to establish their function inside the body. The ADMET inheritance of the ligands was studied, making use of aet SAR.[23,24]

PASS computer Program

Prophecy of *Zingiber officinal*e for anti-viral activity was created with the assistance of software, PASS. PASS is a computer system based program utilized for the prognosis of various sorts of physiological actions for multiple compounds consisting of phytoconstituents. The estimated activity of a substance is predicted as probable activity (Pa) and probable inactivity (Pi). The substances revealing Pa higher than Pi are actually the only components thought about as feasible for a specific medical activity.[25-27]

RESULTS

Drug likeliness Properties

The physicochemical properties of the chosen nine active compounds were studied on DruLi to software. All the compounds obeyed Lipinski's rule (Table 1). Shogasulphonic acid A, gingerenone B shows higher TPSA (138.74, 85.22) and AMR (61.16, 61.4) with suitable HBA, HBD and RB (Table 1). TPSA, as well as AMR, are fundamental physicochemical properties mostly entailed in drug absorption, transport and penetratn mechanism.[28]

Molecular Docking Studies

To discover a prospective candidate for COVID-19, molecular docking work was carried out on 42 phytoconstituents acquired from Z. Officinal binding pocket COVID-19 (PDB ID: 6LU7). These 42 substances were docked towards the COVID-19 target enzyme and rated based on their dock performance. Compounds with a dock value of -6.0 or less are deemed a great example for COVID-19 control. For a detailed review, refer to Table 2. This table displays the number of active molecules acquired after docking. These active molecules have a dock value of -6.0 or lower. Total of 10 compounds was chosen based on 6LU7 binding interactions. Shogasulphonic acid A demonstrated the best-docked score (-6.9 Kcal/mol) with SARS-CoV2 Main Proteases.

Molecular Interaction Studies

The rigid docking results were envisioned utilizing Discovery studio for evaluation of communications. The best binding postures of protein-ligand communications were envisioned and charted eThe most st+rongstrongest connection was noticed in the Shogasulphonic acid A with main protease protein

Table 1: Physicochemical properties of the active compounds and accordance with the rules of drug-likeness.

Sr. No.	Ligand	MW	logp	Alogp	HBA	HBD	TPSA	AMR	nRB	MR	No. of Deviations
1	[6]-Paradol	292.17	3.247	-1.686	2	1	63.6	53.72	10	83.59	0
2	[6]-Shogaol	276.17	4.225	-0.875	1	1	46.53	53.97	9	82.91	0
3	Aframodial	318.22	5.062	0.926	3	0	46.67	90.38	5	92.44	0
4	Cedr-8-ene	204.19	6.597	2.484	0	0	0	65.35	0	66.88	0
5	Copaene	204.19	6.499	1.763	0	0	0	64.85	1	67.14	0
6	Gingerenone-A	356.16	3.321	-0.512	1	2	75.99	54.08	9	101.49	0
7	Isogingerenone B	386.17	2.877	-0.564	1	2	85.22	61.4	10	107.98	0
8	Shogasulfonic acid A	438.13	1.417	-1.974	4	3	138.74	61.16	11	112.5	0
9	Zonarene	204.19	5.643	2.299	0	0	0	67.49	1	69.04	0

Table 2: Molecular docking of selected compounds with Main Protease target proteins.

Sr. No	Ligands	Dock Score (Kcal/mol)
		6LU7
1	(+)-Cyclosativene	-5.8
2	(-)-Camphor	-4.6
3	(-)-Germacrene_D	-5.9
4	(-)-Zingiberene	-5
5	(E)-Nerolidol	-4.8
6	(E, E)-alpha-Farnesene	-4.8
7	(S)-6-Gingerol.	-5.9
8	(S)-6-Gingerol	-4.9
9	1,8-Cineole	-5.5
10	1-Dehydro-[10]-gingerdione	-5.3
11	10-Shogaol	-4.8
12	2-Nonanone	-5.1
13	3-Carene	-5.1
14	4(10)-Thujene	-4.5
15	4-Terpineol	-4.6
16	Aframodial	-5.9
17	Borneol	-4.6
18	Cedr-8-ene	-6.2
19	Citronellol	-4.5
20	Copaene	-6
21	Geraniol	-4.5
22	Gingerenone_A	-6.5
23	Isogingerenone_B	-6.4
24	Nerol	-4.9
25	Nonanol	-3.8
26	Safrole	-5.1
27	Sesquithujene	-5.4
28	Shogasulfonic_acid_A	-6.9
29	Terpinolene	-4.9
30	Zingiberenol.	-5.4
31	Zingiberenol	-5.4
32	Zonarene	-6.3
33	[6]-Gingerdione	-5.7
34	[6]-Paradol	-6.1
35	[6]-Shogaol	-6
36	[7]-Paradol	-5.5
37	alpha-Muurolene	-5.7
38	alpha-Pinene	-4.8
39	beta-Bisabolene	-5.6
40	beta-Cadinene	-5.8
41	beta-Santalol	-5.3
42	beta-Sesquiphellandrene	-5.4

complexes. The main protease with shogasulphonic acid A complex formed six hydrogen bond, i.e., ARG A:105; 6.34 A°, GLN A:107; 4.08 A°, GLN A:110; 3.43 A°, 5.02 A°, THR A:111; 3.39 A°, ASP A:295; 3.97 A°, one pi sigma interaction, i.e., ILE A:106; 5.39 A° and one pi alkyl interactions, i.e., VAL A:104; 6.03 A° (Figures 3-6 and Table 3).

Except for Cedr-8-ene, Copaene and Zonarene, remaining all ligands are involved in hydrogen bond formation with protein. In this view, majorly two primary amino acids are mainly engaged in the hydrogen bond interactions, i.e., GLN A:107 A° and THR A:111 A°.

All the ligands are involved in the hydrophobic interactions with the protein. Majorly two primary amino acids are mainly engaged in the hydrophobic bond interacti i.e., VAL A:104: A° and PHE A:294: 294 A°. No ligand forms electrostatic interactions with the protein.

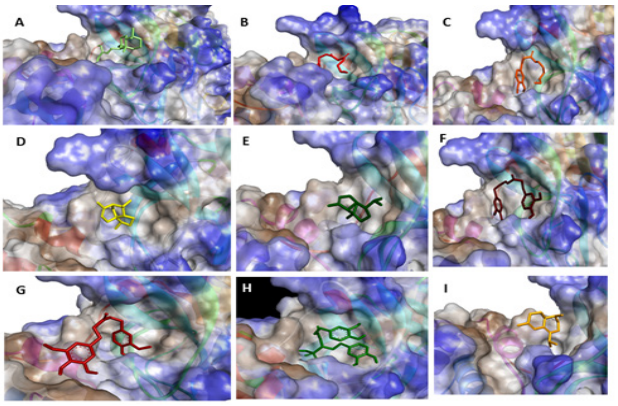

Figure 3: *In silico* Docked complexes of Ligand (Ball and Stick representation) with COVID-19 main protease (6LU7) (Molecular representation) by Biovia Drug Discovery Studio 2019. (A) Aframodial (B) [6]-Paradol (C) [6]-Shogaol (D) Cedr-8-ene (E) Copaene (F) Gingerenone-A (G) Isogingerenone-B (H) Shogasulfonic acid A (I) Zonarene.

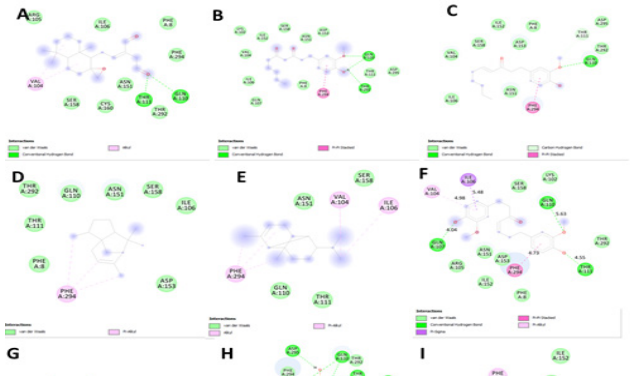

Figure 4: Various Two-dimensional Interactions of ligands with COVID-19 main protease (6LU7). (A) Aframodial (B) [6]-Paradol (C) [6]-Shogaol (D) Cedr-8-ene (E) Copaene (F) Gingerenone-A (G) Isogingerenone-B (H) Shogasulfonic acid A (I) Zonarene.

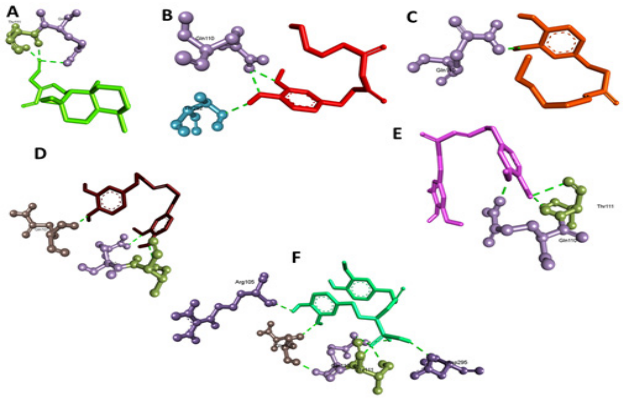

Figure 5: Various three-dimensional Interactions of ligands with COVID-19 main protease (6LU7) via Hydrogen Bond (A) Aframodial (B) [6]-Paradol (C) [6]-Shogaol (D) Gingerenone-A (E) Isogingerenone-B (F) Shogasulfonic acid A.

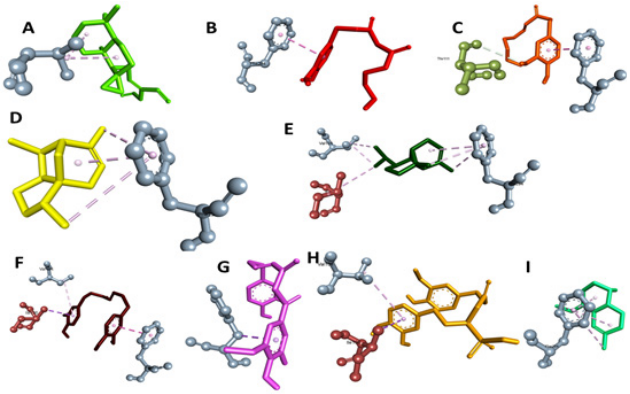

Figure 6: Various three-dimensional Interactions of ligands with COVID-19 main protease (6LU7) via Hydrophobic Interactions. (A) Aframodial (B) [6]-Paradol (C) [6]-Shogaol (D) Cedr-8-ene (E) Copaene (F) Gingerenone-A (G) Isogingerenone-B (H) Shogasulfonic acid A (I) Zonarene.

ADME/T evaluation by using admet SAR

The ADMET properties of the ligands were assessed, making use of admet SAR. ADMET properties for the substances in the research study were evaluated, making use of admet SAR. All the substances revealed excellent human intestinal absorption (HIA), blood-brain barrier (BBB) infiltration. No medication was cancer-causing. All the compounds were AMES negative. The results of HIA, BBB, LD_{50} values for the compounds are listed in Table 4.

PASS predictions for anti-viral activity

The biological activity spectra of previously identified phytoconstituents were obtained by online PASS version. These predictions were interpreted and used in a flexible manner and given in Table 5. 6-Paradol, 6-shagaol, cedr-8-ene, gingerenone-A, Isogingerenone-B and Zonarene showed values Pa > Pi against various viruses.

DISCUSSION

CoronavirusesCorona viruses have a long history of infecting humans and animals and causing respiratory, digestive, liver and central nervous system disses in them.[29] A novel newly emerged SARS-CoV-2 is presenting major threats health noways nowadays.[30] The primary focus has been on clinical management which includes the prevention of infection, control measures and supportive care. Currently, no specific clinical therapeutics are available for the treatment of SARS-CoV-2-medied infections.[31] Thus, the need of the hour

Table 3: Interactions of COVID-19 Main Protease amino acid residues with ligands at receptor sites

Ligands	Binding Affinity, ΔG (Kcal/mol)	Amino acids involved and Distance (A°)	
		Hydrogen Binding Interactions	Hydrophobic Interactions
Aframodial	-6.1	THR A:111 (3.45), GLN A:110 (3.79)	VAL A:104 (5.62. 5.63)
[6]-Paradol	-6.1	GLN A:110 (4.27,5.53), THR A:292 (3.62)	PHE A:294 (4.84)
[6]-Shogaol	-6	GLN A:110 (4.34)	THR A:111 (3.83). PHE A:294 (4.88)
Cedr-8-ene	-6.2	-	PHE A:294 (5.16; 521; 5.45)
Copaene	-6	-	VAL A:104 (4.50,4.67), ILE A:106 (5.17),PHE A:294 (4.09, 4.60,6.20)
Gingerenone-A	-6.5	GLN A: 107 (4.04), GLN A:110 (3.79), THR A:111 (4.55)	VAL A:104 (4.98), ILE A:106 (5.48), PHE A:294 (4.73),
Isogingerenone-B	-6.4	THR A:111 (3.36;3.52), GLN A:110 (3.81)	PHE A:294 (4.35)
Shogasulfonic acid A	-6.9	ARG A:105 (6.34), GLN A:107 (4.08),GLN A:110 (3.43, 5.02), THR A:111 (3.39), ASP A:295 (3.97)	VAL A:104 (6.03),ILE A:106 (5.39)
Zonarene	-6.3	-	PHE A: 294 (4.69, 4.75, 4.90, 5.54)

is to identify and characterize novel drug candidate to overcome the health loses caused by SARS-CoV-2.

With this new breakthrough of Mpro structure in COVID-19, it has offered an astounding possibility to recognize the prospective drug candidates for the effective therapy of coronavirus. In this context, natural products have gained importance as potent anti-viral agents duri rent years.[32,33] Considering the immediate need of therapeutics against COVID-19 and services of natural products in drug discovery, we have screened phytoconstituents from *Z. officinale*as novel drug molecules against Mpro, of SARS-CoV-2 for the identification of Mpro inhibitors to provide natural scaffolds for drug development.

Our examination majorly concentrated on exploring for nutraceutical valuable novelconstituents from the herbal plant of *Z. officinale* with suited pharmacological efficiency and minimum toxicity against COVID-19. From this result, the nine selected phytoconstituents from *Z. officinale* is specifically chosen for further study.

Out of 42 candidates, nine compounds displayed a higher binding affinity with least binding energy with the main protease enzyme. Shogasulphonic acid A has a least binding energy of -6.9 Kcal/mol and found to make six hydrogen bonds with five amino acids, i.e., ARG A:105 (6.34), GLN A:107 (4.08), GLN A:110 (3.43, 5.02), THR A:111 (3.39), ASP A:295 (3.97) and one hydrophobic interaction with PHE A:294 (4.35).ept with, ARG A:105: 105, remaining, the bond length of hydrogen bonds is <5 A°, which indicaonding is stronger more substantialand formed stable complexes. Whereas, Gingerenone A has a binding energy of -6.5 kcal/mol, associates with three hydrogen bonds with GLN A: 107 (4.04), GLN A:110 (3.79), THR A:111 (4.55) and hydrophobic interactions with VAL A:104 (4.98), ILE A:106 (5.48), PHE A:294 (4.73). These two compounds have the least binding affinity in comparison with other ligands due to the formation of more hydrogen bonds with the proteins. All the ligands are involved in hydrophobic interactions; mainly, twacids were involvedined, i.e., PHE A:294: 294, VAL A:104 and ILE A:106.

Lipinski's five-rule is a primary standard for assessing drug likeliness. Lipinski's law specifies the molecular properties essential to the pharmacokinetics of medication in the human bs ADME. Lipi 'sLipinski's law rule of five cond optimal medicationmedicines. Three or more breaches do not meet with the drug likeliness requirements and are not considered to continue product exploration. ADME analyses of selected nine compounds show that all met these ADME check screens (Table 3). This preliminary screening of possible molecules (anti-virals) will help to provide rapid *in-silico* analysis for SARSCoV2 (COVID-19) therapy production.

Thus, we anticipate that the consumption of *Z. officinale* has the potential to boost immunity to fight against COVID-19 infections.

CONCLUSION

In this research study, we have actually made use of Bioinformatics resources, PyRx and also Autodock-Vina to identify the potent molecules from *Z. officinale* against COVID-19 Main Proteases, which participate in a vital part in Coronavirus propagation. Our results propose that the nine phytoconstituents which include [6]-Paradol,[6]-Shogaol, Cedr-8-ene, Copaene, Gingerenone A, Isogingerenone B, Shogasulfonic acid A and Zonarenebe made use of as potential inhibitors of COVID-19 Main Proteases, which may be additionally discovered to examine against Coronavirus (COVID-19) in *in-vitro*, pre-clinical and also clinical tria

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CONFLICT OF INTEREST

The authors declare no conflict of interest

ABBREVIATIONS

Mpro: Main Protease; *Z. officinale: Zingiber officinale*; **SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2; **NCBI:** National Center for Biotechnology Information; **ACE2:** Angiotensin-converting enzyme; **PDB:** Protein DataBase; **DruLiTo:** Drug Likeliness Tool; **PASS:** Prediction of Activity Spectra for Substances; **TPSA:** topological polar surface area; **AMR:** Atom Molar Refractivity; **HBA:** Hydrogen bond acceptor; **HBD:** Hydrogen bond donor; **BBB:** Blood-Brain Barrier; **HIA:** human intestinal absorption; **LD_{50}:** Lethal Dose, 50%.

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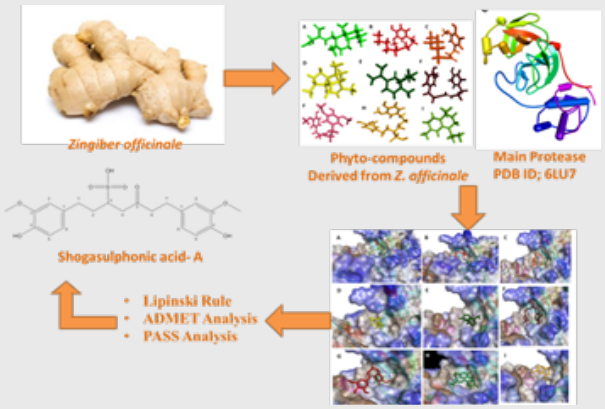
PICTORIAL ABSTRACT



SUMMARY

- Current coronavirus disease (COVID-19) pandemic worldwide is synonymous with 'Severe acute respiratory syndrome' (SARS-CoV2) in humans.
- In this context, the phytoconstituents from Z. officinale were screened against the Main Protease,
- Based on the binding energy levels, nine phytocompounds has been chosen and out of all Shogasulphonic acid displayed the lowest binding energy of -6.9 Kcal/mol.
- All the compounds obeyed Lipinski's rule and none of them is carcinogenic in nature.

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