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An *In Silico* Screening on *Piper nigrum, Syzygium aromaticum* and *Zingiber officinale roscoe* Derived Compounds Against SARS-CoV-2: A Drug Repurposing Approach

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Abstract: As of now, Coronavirus (COVID-19) is spreading overall quickly, and its control is troublesome because there is no compelling immunization or medications accessible in the medical sector. This contagious disease has been associated with numerous respiratory issues. Thus, there is a crucial need to elucidate plant-derived compounds that display inhibitory potential against potential targets of coronavirus and boost the human body's immunity. This infection can contaminate the individuals and cause diseases of the respiratory lot. This research has focused on exploiting the medicinal properties of phytocompounds of three plants that have shown significant anti-inflammatory potential and had been effective against numerous respiratory disorders. This research's main objective was to study the inhibitory potential of these selected twenty-seven phytocompounds derived from *Piper nigrum*, *Syzygium aromaticum*, and *Zingiber officinale roscoe* against protease of COVID-19. We performed screening of selected phytocompounds with antivirus action by employing different *in silico* approaches, including Lipinski rule of five, adme analysis, and molecular docking tools. In silico investigation has revealed the inhibitory potential of these selected ligands (phytocompounds), two crucial targets of coronavirus, including 6LU7 and 7JTL. Out of 27 selected phytocompounds guaiol and gingeronone A has displayed significant inhibitory potential against coronavirus's selected targets. Thus our research findings strongly recommended that phytocompounds derived from black pepper, clove, and ginger could be very useful in battling the COVID-19 pandemic era.

Keywords: COVID-19; black pepper; clove; ginger; 7JTL; 6 LU7; molecular docking; drug repurposing.

1. Introduction

COVID-19 contamination was first depicted in December 2019 in Wuhan, China. Since at that point, this ailment has dispersed through most nations worldwide and as of now caused in excess 9 lakhs fatalities [1]. The causative operator of COVID-19, for example, Serious Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), is a novel beta-corona infection that imparts similitudes to SARS and Middle East Respiratory Syndrome (MERS) infections, which were beforehand answerable for endemics [2-5]. Current treatments are mainly focusing on helicase, protease, immunomodulators, and polymerase, including interferons and corticosteroids [6-9], even though RT-PCR remains the reference standard for making an authoritative finding of COVID-19 disease. Also, bioinformatics plays an important role in

designing new drugs, which would effortlessly help decrease the hour of the investigation, probability of mistake, and the significant expense of clinical and research center preliminaries [10-12]. One of the novel helpful methodologies utilized for the restraint of infection disease is looking for an inhibitor of the protein in normal mixes as they have insignificant results. So, our study was focused on Black pepper (*Piper nigrum*), Clove(*Syzygium aromaticum*), and Ginger(*Zingiber officinale roscoe*). The physical and chemical properties of derived compounds have the capacity to impede the development of protein and hereditary material in the virus infection. Black pepper, clove, and ginger have anti-inflammatory, antibacterial, antiviral, and other healthful properties [13-18]. Continuing exploration, our current examination is intended to discover influential regular helpful specialists from black pepper, clove, and ginger that could show better inhibitory viability against the principle protease of COVID-19 by utilizing the molecular docking approach. This examination's aftereffects will furnish better chances to different specialists with better approaches to perceive and improve new COVID-19 treatment. Until any precise treatment philosophy is accessible for COVID-19, the utilization of subsidiaries of recently realized antiviral medications is a helpful procedure. In this investigation, docking studies were performed over restricting the pocket of COVID-19 to locate the likely little particle to battle perilous COVID-19 illness.

2. Materials and Methods

2.1. Tools requirements for in-silico analysis.

Windows 7 or Windows 10, MGL tools, Discovery Studio Visualizer, Autodock 4.2, Cygwin, Binary files

2.2. Preparation of receptor (target structure).

The objective utilized for docking is the significant protease of the novel COVID-19 and SARS-CoV-2. Their 3D structures were downloaded from PDB (Protein Data Bank), having PDB ID: 6LU7 and 7JTL in pdb format (PDB url:-www.rcsb.org). During target preparation, water particles were eliminated.

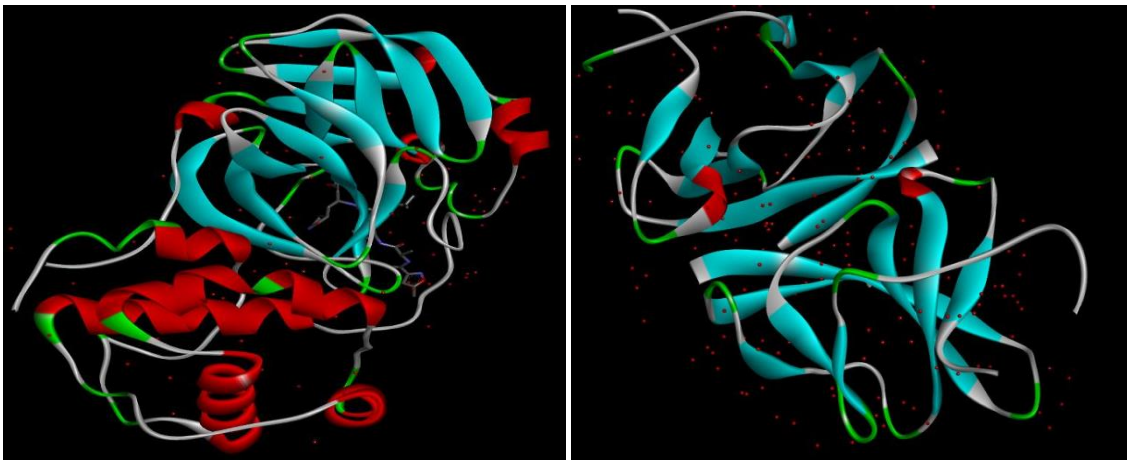


Figure 1. 3-dimensional structure of COVID-19 targets (A) 6LU7 and (B) 7JTL selected for docking analysis.

2.3. Ligand selection and preparation.

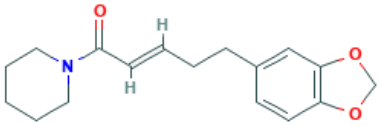
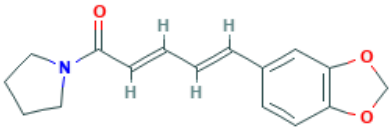
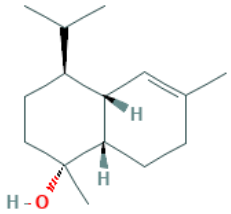
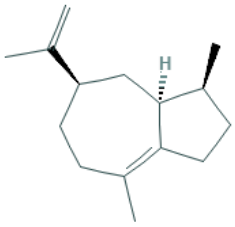
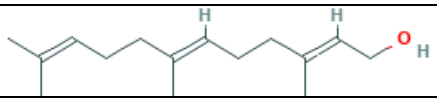
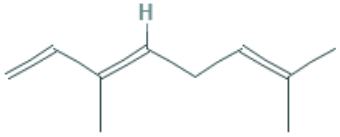
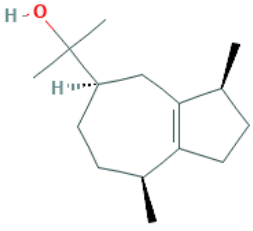
Compounds possessing antiviral activity from Black pepper (*Piper nigrum*), Clove (*Syzygium aromaticum*), and Ginger (*Zingiber officinale roscoe*) were selected for docking

analysis. Their 3-Dimensional structures were obtained from PubChem in .sdf format (PubChem url:- https://pubchem.ncbi.nlm.nih.gov/).

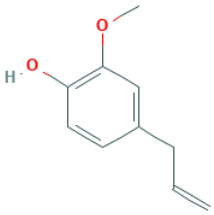
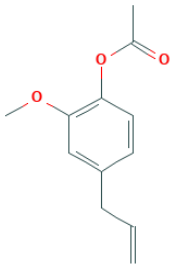
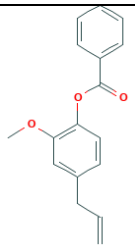
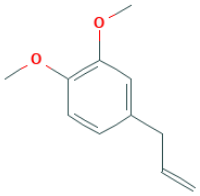
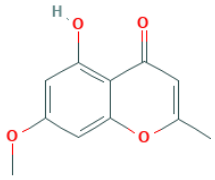
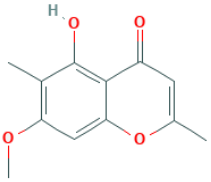
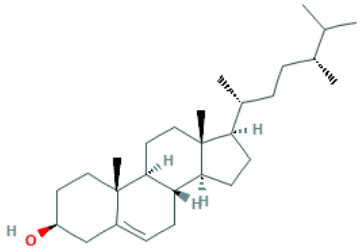
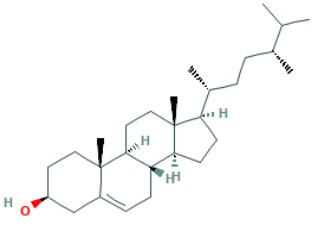
2.4. Lipinski's rule of five.

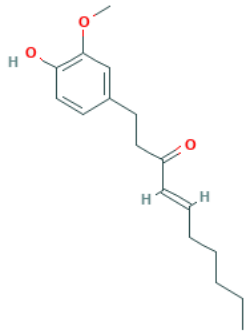
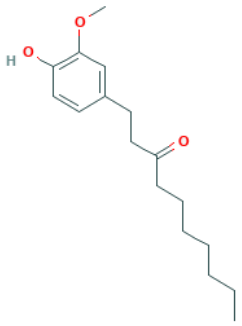
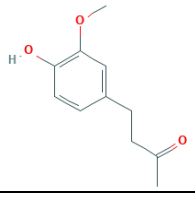
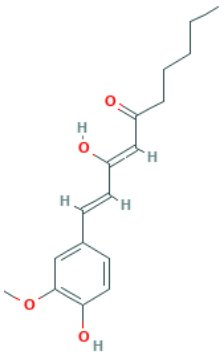
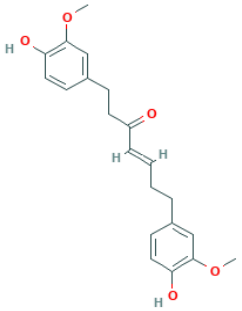
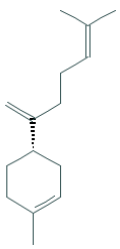
All the compounds were evaluated for their oral bioavailability and medication likeliness properties by Lipinski's standard of five [19-20]. The natural mixes of black pepper, clove, and ginger are picked for docking analysis. The chemical structures of these compounds, along with their PubChem ID, are given in Table 1. These whole sets of preliminary screening probably affect the pharmacokinetics adequacy of medications [Table 2]. Further docking studies were executed according to the protocol described by Khan et al., 2019 [21].

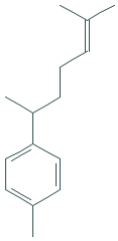
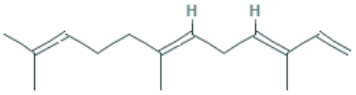
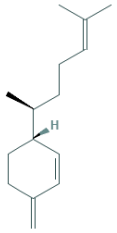
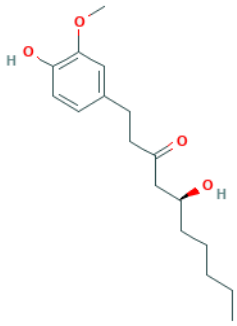
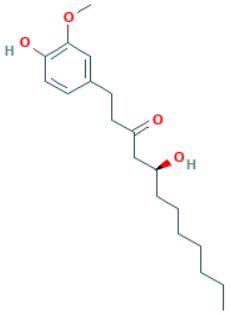
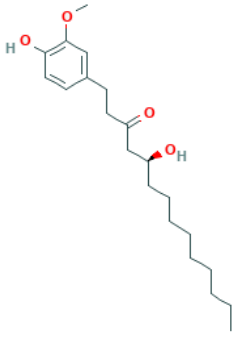
Table 1. Compounds of various compounds from Black pepper (*Piper nigrum*), Clove (*Syzygium aromaticum*), and Ginger (*Zingiber officinale roscoe*).

S.no	Compound name	PubChem ID	Chemical Structure
1.	Piperanine	5320618	
2.	Piperylin A	636537	
3.	Delta cadinol	3084311	
4.	Delta guaiene	94275	
5.	(Z)(E) farnesol	445070	
6.	(E)beta ocimene	5281553	
7.	Guaiol	227829	

Phytocompounds of *Syzygium aromaticum* (clove)

S.no	Compound name	PubChem ID	Chemical Structure
8.	Eugenol	3314	
9.	Eugenol acetate	7136	
10.	Eugenol benzoate	62362	
11.	Methyl eugenol	7127	
12.	Triterpenoids	71597391	
13.	Eugenin	10189	
14.	Eugenitin	3083581	
15.	Campesterol	173183	

S.no	Compound name	PubChem ID	Chemical Structure
Phytocompounds of *Zingiber officinale roscoe* (ginger)			
16.	Shogaol	5281794	
17.	Paradol	94378	
18.	Zingerone	31211	
19.	6-dehydrogingerdione	22321203	
20.	Gingeronone A	5281775	
21.	beta-bisabolene	10104370	

S.no	Compound name	PubChem ID	Chemical Structure
22.	alpha-curcumene	92139	
23.	alpha-farnesene	5281516	
24.	beta-sesquiphellandrene	12315492	
25.	6-Gingerol	442793	
26.	8-Gingerol	168114	
27.	10-Gingerol	168115	

2.5. Docking procedure.

Auto dock 4.2 software was utilized to perform target-ligand docking. Scoring of the target-ligand association was done based on free binding energy [22]. The Lamarckian hereditary calculation (LGA) was applied to elucidate the collaboration design between the COVID-19 and the natural compounds of black pepper ginger and clove [23]. In all docking strategies, 10 free hereditary calculations were run. A population size of 150 for every atom

under investigation LGA pursue was halted the greatest number of 2500000 energy assessments and 27,000 most extreme ages. The auto dock was then executed to acquire Docking Log Files (DLG) for additional examination.

2.6. ADME analysis property.

The ADME parameters of the various compounds from Black pepper (*Piper nigrum*), Clove (*Syzygium aromaticum*), and Ginger (*Zingiber officinale roscoe*) that indicated best outcomes were investigated by SwissADME (SwissADME url:- http://www.swissadme.ch) [24].

3. Results and Discussion

The medication resemblance properties, for example, an atomic load of the compound (Molecular Weight), number of hydrogen bond donor (HBD) and acceptor (HBA), and determined LogP of *Piper nigrum*, *Syzygium aromaticum*, and *Zingiber officinale roscoe* derived compounds, were initially assessed by Lipinski's standard of five. Table 4, 5, and 6 listed the medication resemblance properties of *Piper nigrum*, *Syzygium aromaticum*, and *Zingiber officinale roscoe*. According to Lipinski's rule of five:

- ✓ Molecular weight of the compound should be less than 500 daltons
- ✓ Hydrogen bond accepter range should be less than 10
- ✓ Hydrogen bond donor range should be less than 5
- ✓ And the value of Log P should be less than 5

3.1. Selection of screened phytocompounds for docking studies.

In order to screen a potential lead candidate for COVID-19 treatment, we have selected 26 compounds from Black pepper (*Piper nigrum*), Clove (*Syzygium aromaticum*), and Ginger (*Zingiber officinale roscoe*) for this study. A literature review has supported the significant inhibitory potential of these phytocompounds against various viral diseases such as HIV and Hepatitis, through various ways such as inhibition of reverse-transcriptase, DNA polymerase, and protease, etc. We have considered two standard drug references for our study, including Abacavir and hydroxychloroquine, as they are presently being utilized for COVID-19 treatment [25-26].

Table 2. Chemical and physical properties of various compounds from Black pepper (*Piper nigrum*), Clove (*Syzygium aromaticum*), and Ginger (*Zingiber officinale roscoe*).

Compound Name	Pub chem id	Molecular wt.	Hydrogen bond accepter	Hydrogen bond donor	Log p
Piperanine	5320618	287.35 g/mol	3	0	3.1
Piperylin A	636537	271.31 g/mol	3	0	3.1
Delta cadinol	3084311	222.37 g/mol	1	1	3.3
Delta guaiene	94275	204.35 g/mol	0	0	4.6
(Z)(E) farnesol	445070	222.37 g/mol	1	1	4.8
(E) beta ocimene	5281553	136.23 g/mol	0	0	4.3
Guaiol	227829	222.37 g/mol	1	1	3.1
Eugenol	3314	164.2 g/mol	2	1	2
Eugenol acetate	7136	206.24 g/mol	3	0	2.3
Eugenol benzoate	62362	268.31 g/mol	3	0	4.4
Methyl eugenol	7127	178.23 g/mol	2	0	2.5
Triterpenoids	71597391	472.7 g/mol	5	4	3.9
Eugenin	10189	206.19 g/mol	4	1	1.2
Eugenitin	3083581	220.22 g/mol	4	1	2.5
Campesterol	173183	400.7 g/mol	1	1	8.8

Compound Name	Pub chem id	Molecular wt.	Hydrogen bond accepter	Hydrogen bond donor	Log p
Shogaol	5281794	276.4 g/mol	3	1	3.7
Paradol	94378	278.4 g/mol	3	1	3.8
Zingerone	31211	194.23 g/mol	3	1	0.8
6-dehydrogingerdione	22321203	290.4 g/mol	4	2	4.2
Gingeronone A	5281775	356.4 g/mol	5	2	3.7
beta-bisabolene	10104370	204.35 g/mol	0	0	5.2
alpha-curcumene	92139	202.33 g/mol	0	0	5.4
alpha-farnesene	5281516	204.35 g/mol	0	0	6.1
beta-sesquiphellandrene	12315492	204.35 g/mol	0	0	5.4
6-Gingerol	442793	294.4 g/mol	4	2	2.5
8-Gingerol	168114	322.4 g/mol	4	2	4.2
10-Gingerol	168115	350.5 g/mol	4	2	5.3

3.2. Molecular docking using AutoDock 4.2 software.

Then we performed molecular docking by using AutoDock tool 4.2. The binding energies and docking results of the derived compounds from black pepper, clove, and ginger against 6LU7 are listed below in tables 7, 8, and 9. Out of 26 selected compounds, Guaiol has shown the best inhibitory potential (maximum binding energy) against the 6LU7 target of COVID-19 (Table 3). Gingeronone A has shown the best inhibitory potential (maximum binding energy) against the 7JTL target of COVID-19 (Table 4) (Figure 2). Additionally, comparative analysis of these two compounds with standard drugs has also depicted better inhibitory potential (maximum binding energy) against these two targets (Table 5 & Table 6) (Figure 3 & Figure 4). Thus both the screened phytocompounds could be further utilized for *in vitro* studies to elucidate a potent lead candidate for drug development against COVID-19.

Table 3. Docking results of 6LU7 (COVID-19) with several compounds of black pepper, clove, and ginger.

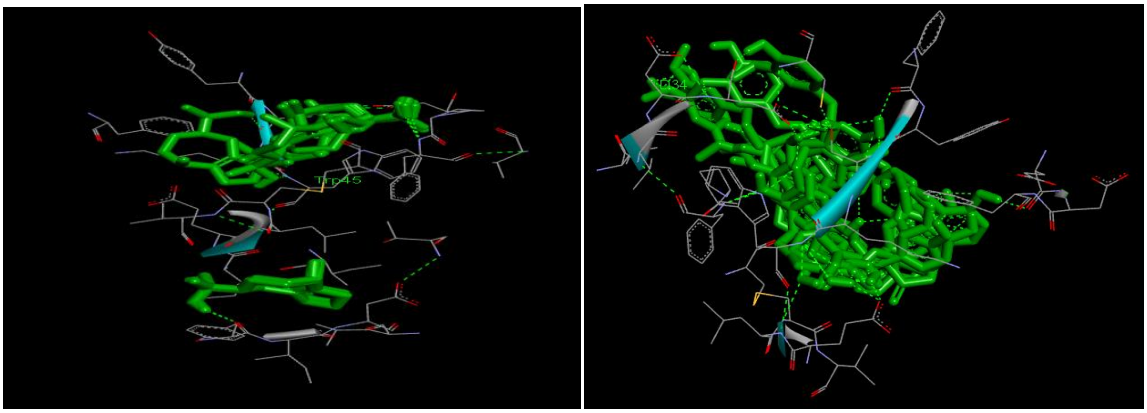
S.no	Compounds	Autodock				
		Binding Energy (kcal/mol)	**No. of hydrogen bonds**	**Total Internal Energy**	**Estimated inhibition constant (Ki)**	**Residues**
1.	Piperanine	-4.54	1	-0.41	470.97	Target:A:GLN127:HN
2.	Piperylin A	-4.88	2	-0.17	264.24	Target:A:GLN107:HN Target:A:ILE152:O
3.	Delta cadinol	-6.42	2	-0.2	19.67	Target:A:THR111:HN: Target:A:THR111:OG1
4.	Delta guaiene	-5.73	…….	0.17	63.59	……..
5.	(Z)(E) farnesol	-3.52	3	-0.58	2.62	Target:A:ALA129:HN: Target:A:LYS137:HN: Target:A:ALA129:O
6.	(E) beta ocimene	-3.51	…….	-0.17	2.64	……
7.	**Guaiol**	**-6.50**	2	-0.19	17.13	Target:A:THR111:HN: Target:A:THR111:OG1
8.	Eugenol	-4.85	3	-0.27	280.63	Target:A:THR111:HN: Target:A:GLN110:HE21 Target:A:THR111:OG1
9.	Eugenol acetate	-4.66	2	-0.4	382..51	Target:A;GLN110:HE21 Target:A:THR111:HN:
10.	Eugenol benzoate	-4.41	1	-0.92	587.85	Target:A:GLN127:O
11.	Methyl eugenol	-4.35	1	-0.38	649.74	Target:A:GLN110:HE21
12.	Triterpenoids	-5.53	2	-0.37	87.89	Trget:A:LYS5:HZ3: Target:A:GLY170:O
13.	Eugenin	-4.76	2	-0.55	326.61	Target:A:GLN110:HE21 Target:A:THR111:HN:
14.	Eugenitin	-5.22	1	-0.59	150.18	Target:A:GLN110HE21:
15.	Campesterol	-4.41	……	-0.9	251.61	……..
16.	Shogaol	-4.12	2	-1.37	962.19	Target:A:GLU290:OE1 Target:A:LYS5:HZ2

S.no	Compounds	Autodock				
		Binding Energy (kcal/mol)	No. of hydrogen bonds	Total Internal Energy	Estimated inhibition constant (Ki)	Residues
17.	Paradol	-3.43	…..	-1.22	3.06	…….
18.	Zingerone	-5.30	4	-0.34	131.04	Target:A:THR111:HN: Target:A:SER158:HG: Target:A:GLN110:HE21 : Target:A:THR111:OG1
19.	6-dehydrogingerdione	-4.55	1	-0.75	461.48	Target:A:ARG105:O
20.	Gingeronone A	-4.8	1	-1.76	305.41	Target:A:GLY138:O
21.	beta-bisabolene	-4.07	……	-0.49	1.04	……..…
22.	alpha-curcumene	-4.64	……..	-0.6	394.74	……
23.	alpha-farnesene	-4.1	……..	-0.33	958.18	……
24.	beta-sesquiphellandrene	-5.43	…….	-0.73	103.95	…….
25.	6-Gingerol	-3.21	1	-1.38	4.46	Target:A:LYS5:HZ2:
26.	8-Gingerol	-3.22	2	-1.31	4.38	Target:A:LYS5:HZ2: Target:A:GLU290:O
27.	10-Gingerol	-2.53	1	-1.93	13.95	Target:A:LYS137:O

Table 4. Docking results of 7JTL (SARS Cov-2) with several compounds of black pepper, clove, and ginger.

S.no	Compounds	Autodock				
		Binding Energy (kcal/mol)	No. of hydrogen bonds	Total Internal Energy	Estimated inhibition constant (Ki)	Residues
1	Piperanine	-6.66	2	-0.36	13.22	Target:A:VAL33:O Target:A:CYS61:HN:
2	Piperylin A	-6.55	2	-0.29	14.71	Target:A:TRP45:HN: Target:A:CYS61:HN:
3	Delta cadinol	5.94	1	-0.2	44.55	Target:A:LEU60:O
4	Delta guaiene	-5.98	…….	-018	41.45	……..
5	(Z)(E) farnesol	-5.72	3	-0.55	64.55	Target:A:TRP45:HN: Target:A:CYS61:HN: Target:A:TRP45:O
6	(E) beta ocimene	-4.09	……..	-0.26	1.00	…….
7	Guaiol	-6.38	1	-0.18	21.21	Target:A:TYR73:O
8	Eugenol	-5.33	1	-0.48	123.29	Target:A:CYS61:HN:
9	Eugenol acetate	-5.08	3	-0.46	189.60	Target:A:CYS61:HN: Target:A:TRP45:HN: Target:A:SER43:O
10	Eugenol benzoate	-6.19	2	-0.73	28.80	Target:A:TRP45:HE1: Target:A:PHE86:HN:
11	Methyl eugenol	-4.82	2	-0.35	294.39	Target:A:TRP45:HE1: Target:A:PHE86:HN:
12	Triterpenoids	-6.12	2	-0.41	32.92	Target:A:VAL33:O Target:A:PHE86:O
13	Eugenin	-5.97	1	-0.57	42.28	Target:A:CYS61:HN:
14	Eugenitin	24.73	2	-0.58		Target:A:LEU60:HN: Target:A:CYS61:HN:
15	Campesterol	-7.23	……	-0.75	5.00	……
16	Shogaol	-5.96	1	-1.16	42.48	Target:A:PHE86:HN:
17	Paradol	-5.16	1	-1.08	165.48	Target:A:PHE86:HN:
18	Zingerone	-5.74	2	-0.56	62.84	Target:A:CYS61:HN: Target:A:PHE86:HN:
19	6-dehydrogingerdione	-5.85	1	-1.26	51.75	Target:A:TRP45:HN:
20	Gingeronone A	**-7.65**	2	-1.36	2.49	Target:A:TRP45:HN: Target:A:ASP35:OD2
21	beta-bisabolene	-5.89	……	-0.41	47.99	……
22	alpha-curcumene	-5.58	…….	-0.35	81.87	……
23	alpha-farnesene	-5.45	…….	-0.39	101.72	……..

S.no	Compounds	Autodock				
		Binding Energy (kcal/mol)	No. of hydrogen bonds	Total Internal Energy	Estimated inhibition constant (Ki)	Residues
24	beta-sesquiphellandrene	-6.13	……..	-0.58	31.98	…….
25	6-Gingerol	-4.27	1	-1.1	736.81	Target:A:PHE86:HN
26	8-Gingerol	-4.7	2	-1.16	356.1	Target:A:TRP45:HN: Target:A:SER43:O
27	10-Gingerol	-5.66	1	-1.18	71.05	Target:A:CYS61:HN:

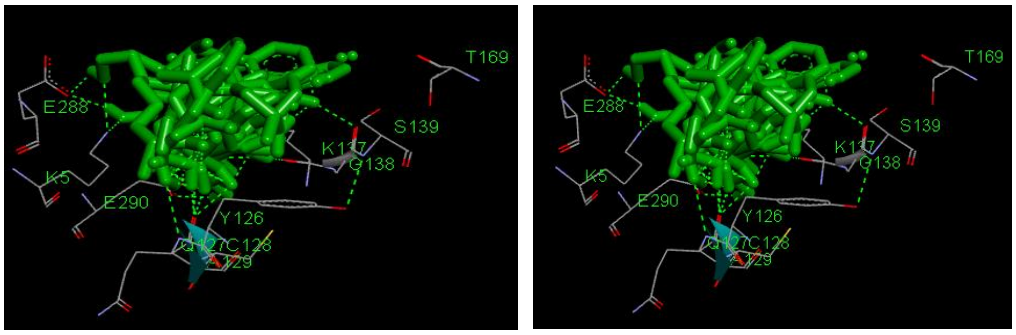


Guaiol Gingeronone-A

Figure 2. Best screened compound showing maximum binding energy against two selected targets of co (a) 6LU7 and (b)7JTL binding with black pepper, clove, and ginger has shown the best binding energies.

Table 5. Docking results of 6LU7 (COVID-19) with hydroxychloroquine.

S.No	Compounds	Autodock				
		Binding Energy (kcal/mol)	No. of hydrogen bonds	Total Internal Energy	Estimated inhibition constant (Ki)	Residues
1	**Hydroxychloroquine**	-3.81	……	-2.6	1.61	…….
2	**Remdesivir**	-3.52	2	-2.73	2.63	Target:A:GLY138:O Target:A:LYS137:O

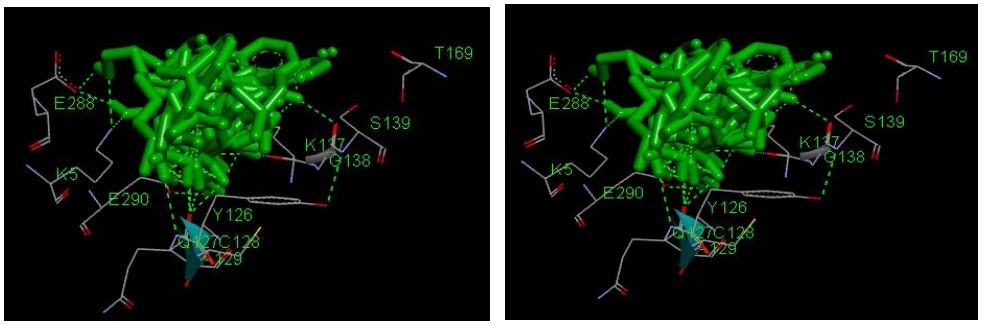


(a) (b)

Figure 3. Docking analysis of 6LU7 with two standard drugs (a) Hydroxychloroquine and (b) Remdesivir.

Table 6. Docking results of 7JTL (SARS Cov-2) with hydroxychloroquine.

S.No	Compounds	Autodock				
		Binding Energy (kcal/mol)	No. of hydrogen bonds	Total Internal Energy	Estimated inhibition constant (Ki)	Residues
1	**Hydroxychloroquine**	-5.56	2	-0.3	84.47	Target:A:GLU59:OE 2 Target:A:GLU106:O
2	**Remdesivir**	-3.15	1	0.01	4.94	Target:A:CYS83:O



(a) (b)

Figure 4. Docking analysis of 6LU7 with two standard drugs (a) Hydroxychloroquine and (b) Remdesivir.

4. Conclusions

Our current investigation endeavored to investigate the capability of successful natural mixes from black pepper, clove, and ginger against the principle protease of COVID-19 in contrast with the proposed drug hydroxychloroquine and remdesivir. We have chosen powerful natural mixes from these black pepper, clove, and ginger against COVID-19 objective protein 6LU7 and 7JTL. Our outcomes from molecular docking strongly suggested that Guaiol and Gingeronone A showed the best restricting viability against COVID-19 Main Proteases, which can urge us to analyze its potential in pre-clinical and clinical examinations.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Zu, Z.Y.; Jiang, M.D.; Xu, P.P.; Chen, W.; Ni, Q.Q.; Lu, G.M.; Zhang, L.J. Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology* **2020**, *296*, E15-E25, https://doi.org/10.1148/radiol.2020200490.
2. Abdirizak, F.; Lewis, R.; Chowell, G. Evaluating the potential impact of targeted vaccination strategies against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in the healthcare setting. *Theoretical Biology and Medical Modelling* **2019**, *16*, https://doi.org/10.1186/s12976-019-0112-6.
3. Hosseiny, M.; Kooraki, S.; Gholamrezanezhad, A.; Reddy, S.; Myers, L. Radiology Perspective of Coronavirus Disease 2019 (COVID-19): Lessons From Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome. *American Journal of Roentgenology* **2020**, *214*, 1078-1082, https://doi.org/10.2214/AJR.20.22969.
4. Momattin, H.; Mohammed, K.; Zumla, A.; Memish, Z.A.; Al-Tawfiq, J.A. Therapeutic Options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – possible lessons from a systematic review of SARS-CoV therapy. *International Journal of Infectious Diseases* **2013**, *17*, e792-e798, https://doi.org/10.1016/j.ijid.2013.07.002.
5. Lee, P.-I.; Hsueh, P.-R. Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV. *Journal of Microbiology, Immunology and Infection* **2020**, *53*, 365-367, https://doi.org/10.1016/j.jmii.2020.02.001.

6. Beigel, J.H.; Tomashek, K.M.; Dodd, L.E.; Mehta, A.K.; Zingman, B.S.; Kalil, A.C.; de Castilla, D.L. Remdesivir for the treatment of Covid-19—preliminary report. *The New England journal of medicine* **2020,** 1-14, https://doi.org/10.1056/NEJMoa2007764.
7. Gao, J.; Tian, Z.; Yang, X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *BioScience Trends* **2020**, *14*, 72-73, https://doi.org/10.5582/bst.2020.01047.
8. Cortegiani, A.; Ingoglia, G.; Ippolito, M.; Giarratano, A.; Einav, S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *Journal of Critical Care* **2020**, *57*, 279-283, https://doi.org/10.1016/j.jcrc.2020.03.005.
9. Wang, T.; Du, Z.; Zhu, F.; Cao, Z.; An, Y.; Gao, Y.; Jiang, B. Comorbidities and multi-organ injuries in the treatment of COVID-19. *The Lancet* **2020**, *395*, https://doi.org/10.1016/S0140-6736(20)30558-4.
10. Liu, Y.; Chan, W. K.; Wang, Z.; Hur, J.; Xie, J.; Yu, H.; He, Y. Ontological and bioinformatic analysis of anti-coronavirus drugs and their Implication for drug repurposing against COVID-19. *Pre print* **2020,** https://doi.org/10.20944/preprints202003.0413.v1.
11. Feng, Z.; Chen, M.; Liang, T.; Shen, M.; Chen, H.; Xie, X.-Q. Virus-CKB: an integrated bioinformatics platform and analysis resource for COVID-19 research. *Briefings in Bioinformatics* **2020**, https://doi.org/10.1093/bib/bbaa155.
12. Huang, X.; He, C.; Hua, X.; Kan, A.; Sun, S.; Wang, J.; Li, S. Bioinformatic Analysis of Correlation between Immune Infiltration and COVID-19 in Cancer Patients. *International Journal of Biological Sciences* **2020**, *16*, 2464-2476, https://doi.org/10.7150/ijbs.48639.
13. D'Souza, S.P.; Chavannavar, S.V.; Kanchanashri, B.; Niveditha, S.B. Pharmaceutical Perspectives of Spices and Condiments as Alternative Antimicrobial Remedy. *Journal of Evidence-Based Complementary & Alternative Medicine* **2017**, *22*, 1002-1010, https://doi.org/10.1177/2156587217703214.
14. Yashin, A.; Yashin, Y.; Xia, X.; Nemzer, B. Antioxidant Activity of Spices and Their Impact on Human Health: A Review. *Antioxidants* **2017**, *6*, https://doi.org/10.3390/antiox6030070.
15. Rasool, A.; Khan, M.-u.-R.; Ali, M.; Anjum, A.; Ahmed, I.; Aslam, A.; Rafique, G.; Masood, S.; Nawaz, M. Anti-Avian influenza virus H9N2 activity of aqueous extracts of Zingiber officinalis (Ginger) & Allium sativum (Garlic) in chick embryos. *Pakistan Journal of Pharmaceutical Sciences* **2017**, *30*, 1341-1344.
16. Kaushik, S.; Jangra, G.; Kundu, V.; Yadav, J.P.; Kaushik, S. Antiviral activity of Zingiber officinale (Ginger) ingredients against the Chikungunya virus. *VirusDisease* **2020**, *31*, 270-276, https://doi.org/10.1007/s13337-020-00584-0.
17. Beristain-Bauza, S.D.C.; Hernández-Carranza, P.; Cid-Pérez, T.S.; Ávila-Sosa, R.; Ruiz-López, I.I.; Ochoa-Velasco, C.E. Antimicrobial Activity of Ginger (Zingiber Officinale) and Its Application in Food Products. *Food Reviews International* **2019**, *35*, 407-426, https://doi.org/10.1080/87559129.2019.1573829.
18. Nag, A.; Chowdhury, R.R. Piperine, an alkaloid of black pepper seeds can effectively inhibit the antiviral enzymes of Dengue and Ebola viruses, an in silico molecular docking study. *VirusDisease* **2020**, *31*, 308-315, https://doi.org/10.1007/s13337-020-00619-6.
19. Tice, C.M. Selecting the right compounds for screening: does Lipinski's Rule of 5 for pharmaceuticals apply to agrochemicals? *Pest Management Science* **2001**, *57*, 3-16, https://doi.org/10.1002/1526-4998(200101)57:1<3::AID-PS269>3.0.CO;2-6.
20. Athar Abbasi, M.; Raza, H.; Aziz ur, R.; Zahra Siddiqui, S.; Adnan Ali Shah, S.; Hassan, M.; Seo, S.-Y. Synthesis of novel N-(1,3-thiazol-2-yl)benzamide clubbed oxadiazole scaffolds: Urease inhibition, Lipinski rule and molecular docking analyses. *Bioorganic Chemistry* **2019**, *83*, 63-75, https://doi.org/10.1016/j.bioorg.2018.10.018.
21. Khan, M.F.; Verma, G.; Akhtar, W.; Shaquiquzzaman, M.; Akhter, M.; Rizvi, M.A.; Alam, M.M. Pharmacophore modeling, 3D-QSAR, docking study and ADME prediction of acyl 1,3,4-thiadiazole amides and sulfonamides as antitubulin agents. *Arabian Journal of Chemistry* **2019**, *12*, 5000-5018, https://doi.org/10.1016/j.arabjc.2016.11.004.
22. Castro-Alvarez, A.; Costa, A.M.; Vilarrasa, J. The Performance of Several Docking Programs at Reproducing Protein–Macrolide-Like Crystal Structures. *Molecules* **2017**, *22*, https://doi.org/10.3390/molecules22010136.
23. Guo, S.; Chen, Y.; Shi, S.; Wang, X.; Zhang, H.; Zhan, Y.; An, H. Arctigenin, a novel TMEM16A inhibitor for lung adenocarcinoma therapy. *Pharmacological Research* **2020**, *155*, https://doi.org/10.1016/j.phrs.2020.104721.
24. Tsaioun, K.; Blaauboer, B.J.; Hartung, T. Evidence-based absorption, distribution, metabolism, excretion (ADME) and its interplay with alternative toxicity methods. *Altex* **2016**, *33*, 343-358,https://dx.doi.org/10.14573/altex.1610101.
25. Beigel, J.H.; Tomashek, K.M.; Dodd, L.E.; Mehta, A.K.; Zingman, B.S.; Kalil, A.C.; Hohmann, E.; Chu, H.Y.; Luetkemeyer, A.; Kline, S.; Lopez de Castilla, D.; Finberg, R.W.; Dierberg, K.; Tapson, V.; Hsieh, L.; Patterson, T.F.; Paredes, R.; Sweeney, D.A.; Short, W.R.; Touloumi, G.; Lye, D.C.; Ohmagari, N.; Oh, M.-d.; Ruiz-Palacios, G.M.; Benfield, T.; Fätkenheuer, G.; Kortepeter, M.G.; Atmar, R.L.; Creech, C.B.; Lundgren, J.; Babiker, A.G.; Pett, S.; Neaton, J.D.; Burgess, T.H.; Bonnett, T.; Green, M.; Makowski, M.;

Osinusi, A.; Nayak, S.; Lane, H.C. Remdesivir for the Treatment of Covid-19 — Final Report. *New England Journal of Medicine* **2020**, *383*, 1813-1826, https://doi.org/10.1056/NEJMoa2007764.
26. Pandey, P.; Khan, F.; Rana, A.K.; Srivastava, Y.; Jha, S.K.; Jha, N.K. A Drug Repurposing Approach Towards Elucidating the Potential of Flavonoids as COVID-19 Spike Protein Inhibitors. *Biointerface Research in Applied Chemistry* **2020**, *11*, 8482-8501, https://dx.doi.org/10.33263/BRIAC111.84828501
27. Pandey, P.; Khan, F.; Kumar, A.; Srivastava, A.; Jha, N.K. Screening of Potent Inhibitors Against 2019 Novel Coronavirus (Covid-19) from Alliumsativum and Allium cepa: An In Silico Approach. *Biointerface Research in Applied Chemistry* **2020**, *11*, 7981-7993, https://dx.doi.org/10.33263/BRIAC111.79817993.