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Molecular Docking to Discover Potential Bio-Extract Substitutes for Hydroxychloroquine against COVID-19 and Malaria

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Abstract: ***The goal of the current study is to find an alternative to hydroxychloroquine that is an antimalarial and has in vitro activity against SARS-CoV-2. The crystal structure of the COVID-19 main protease in complex with an inhibitor N3 (6LU7) was used for molecular docking analysis with hydroxychloroquine and phytochemicals with medicinal properties. The novel corona virus (2019-nCoV), family Coronaviridae, genus Beta coronavirus, is thought to be one of the most dangerous pathogenic RNA viruses that causes severe acute respiratory syndrome and is thought to be a threat to humanity. Our research has led to the discovery of two useful phytochemicals that can be obtained from the annual flowering plant Nigella sativa, which is native to the Indian Subcontinent and West Asia. These phytochemicals, longifolene and thymohydroquinone, are suitable alternatives to hydroxychloroquine in the treatment of malaria and COVID-19.***

Keywords: COVID-19, Hydroxychloroquine, Thymohydroquinone, longifolene

1. Introduction

Chinese COV-19 patients have reported that chloroquine and hydroxychloroquine are effective against SARS-CoV-2. In late December 2019, an emerging disease outbreak (COVID-19) was caused by a novel coronavirus (named SARS-CoV-2 latter), which began in Wuhan, China, and quickly spread throughout China and beyond [1, 2]. On March 12, 2020, the WHO proclaimed the COVID-19 outbreak to be a pandemic [3]. In order to stop the spread of the virus throughout the community, it was imperative that symptomatic patients receive an efficient therapy that also shortens the length of viral carriage. Repurposing older medications for use as antiviral therapy is an intriguing tactic among potential COVID-19 therapeutic options because information about drug interactions, posology, safety profile, and adverse effects are widely available [4, 5]. A previous study reported an inhibitor effect of remdesivir, a new antiviral drug, and chloroquine, an old antimalarial drug, on the growth of SARS-CoV-2 in vitro [6]. An earlier clinical trial of COVID-19 Chinese patients revealed that chloroquine significantly affected both clinical outcome and viral clearance when compared to control groups [7]. Chinese specialists advise treating patients with 500 mg of chloroquine twice day for ten days if they have been diagnosed with mild, moderate, or severe instances of COVID-19 pneumonia and do not have any contraindications to the medication. Longifolene is a bicyclic compound that falls under the sesquiterpene category [8]. Numerous plant essential oils contain a broad family of chemical molecules called sesquiterpenes. Thymohydroquinone molecule is a member of the quinones group [9]. It is mostly present in black cumin seeds (Nigella sativa), it is thought to be the primary bioactive element in the essential oil of those seeds [10]. We provide our preliminary findings in this paper, concentrating on virological information in patients receiving hydroxychloroquine in comparison to a control group. Through the use of the Biovia Discovery Studio tool for molecular docking studies, we were able to determine that the phytochemicals Thymohydroquinone and longifolene have similar binding sites and do project similar results to those of hydroxychloroquine. As a result, phytochemicals from Nigella sativa, an annual flowering plant native to the Indian Subcontinent and West Asia, can be obtained. N. Sativa leaves are linear and finely split, and it can grow up to 20–30 cm tall. The fragile flowers typically have five to ten petals and are tinted pastel blue and white.

2. Materials and Methods

a) Structure retrieval

The crystal structure of COVID-19 main protease in complex with an inhibitor N3of novel corona virus was retrieved from RCSB PDB (https: //www.rcsb. org/structure). with PDB ID '6LU7' being selected for the present study.

b) Phytochemical retrieval

The SDF file of compounds was retrieved from PubChem along with SMILES information. The SMILES (Simplified molecular input-line entry system) of each drug were submitted to Molinspiration cheminformatics software tool for QSAR analysis to check for any violations in their ADME properties through RO5 and to predict molecular behaviour. The list of Flavonoids and other compounds were obtained. The SDF files of the ligands were obtained from NCBI Pubchem. The list of the ligands used are Longifolene (CID 1796220), Diallyldisulphide (CID 16590), Tocotrienol (CID 9929901), Cocculin (CID 6473767), Tangeretin (CID 68077), Camphene (CID 6616), Sulphoraphane (CID 336944062), Limonene (CID 22311), P. Cymene (CID 7463), Thymohydroquinone (CID 95779), Allylpropyldisulphide

(CID 16591), Zingiberene (CID 92776), Flavone (CID 10680), Dithymoquinone (CID 398941), Gingerol (CID 442793).

Table 1: The standard properties of Lipinski Rule of 5 (RO5)

S. No.	Properties	Values
1.	cLogP (Partition coefficient)	<5
2.	Molecular weight (MW)	<500
3.	Hydrogen Bond Donors (OHNH)	<5
4.	Hydrogen Bond Acceptors (ON)	<10

Note-Number of violations (n Violations) must be zero.

c) Molecular docking studies and visualization

Binding mode and selectivity of COVID-19 with individual flavonoids, was studied by Molecular Docking Algorithm Based on Shape Complementarity Principles named as PATCHDOCK (https: //bioinfo3d. cs. tau. ac. il/PatchDock/php. php) by selecting clustering RMSD as 1.5 and protein-small ligand complex type and the obtained results were visualized using latest version of visualization software Biovia discovery studio 2019.

d) Evaluation and selection of alternative of hydroxychloroquine

The obtained results were evaluated and common binding sites of the docked compounds were compared to that of hydroxychloroquine.

3. Results

a) Structure retrieval

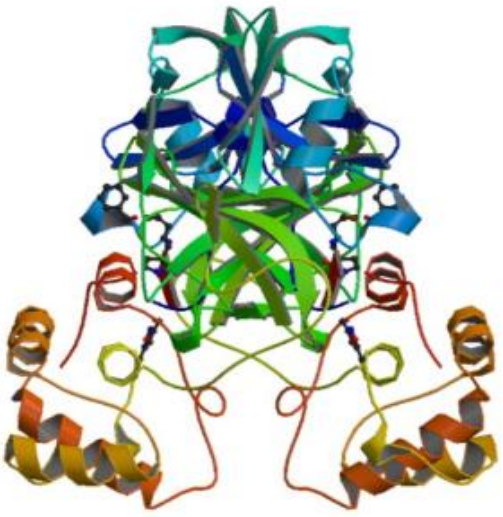


Figure 1: The crystal structure of COVID-19 main protease in complex with an inhibitor N3 (6LU7)

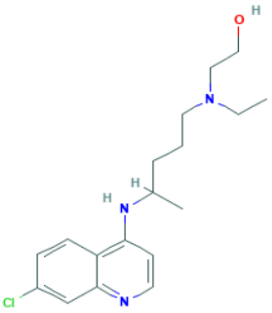
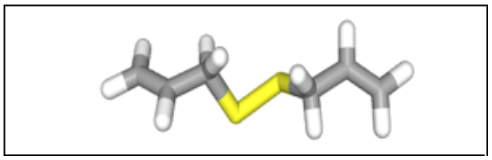


Figure 2: Structure of hydroxychloroquine



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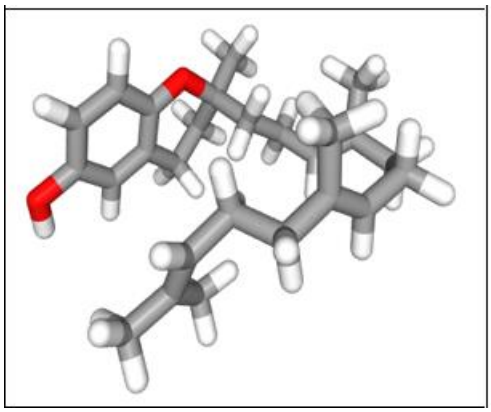

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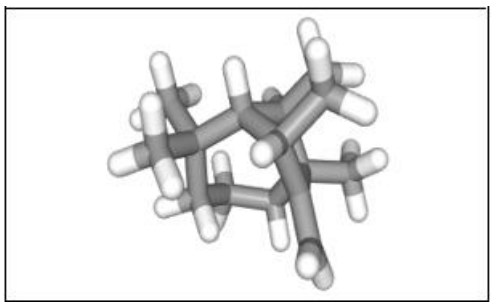

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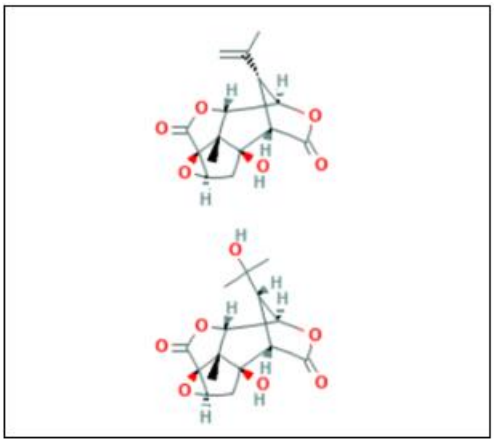

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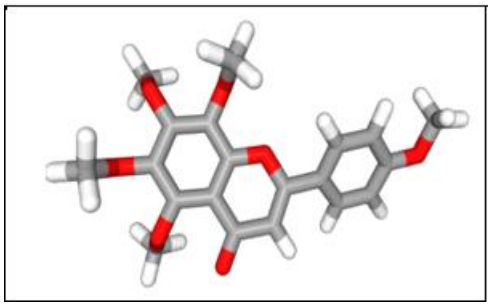
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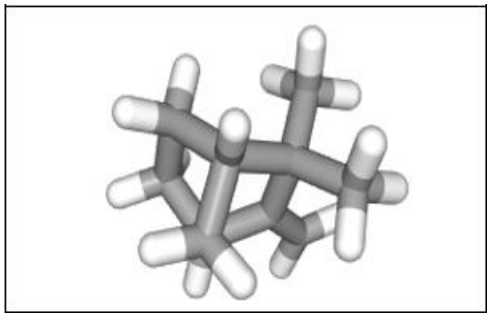
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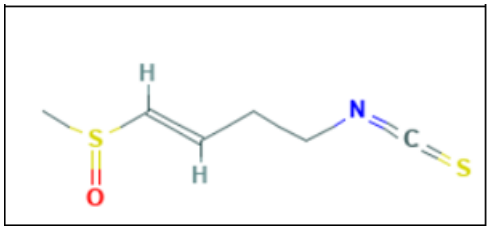

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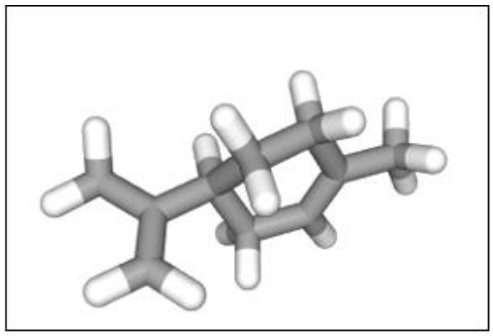
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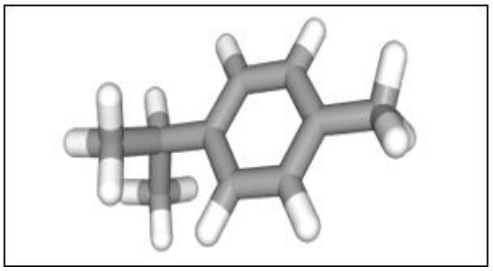
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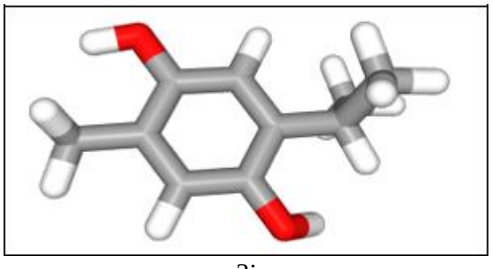
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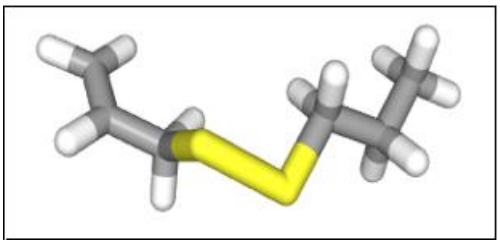
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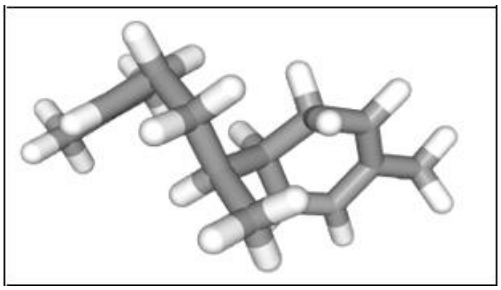
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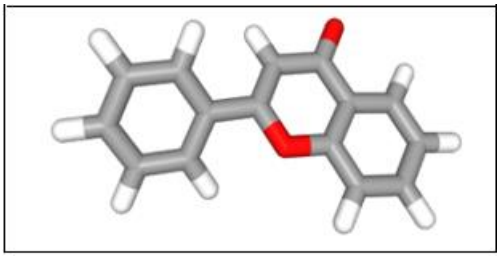
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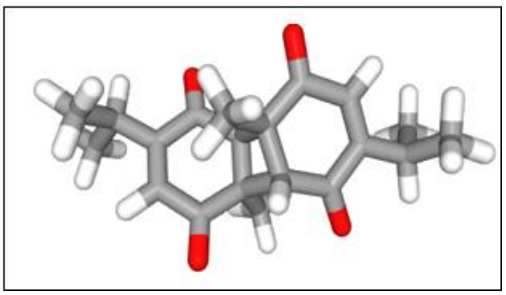
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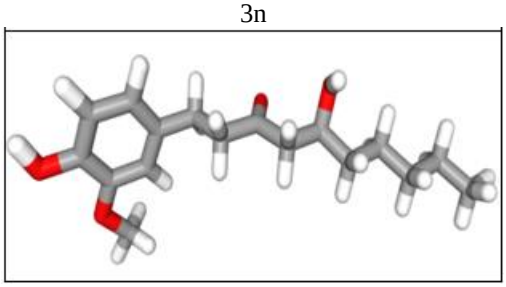

3o

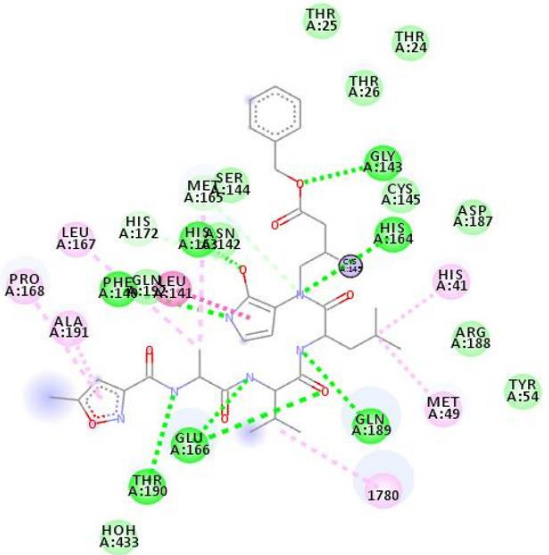
Figure 3: Structure of following compounds – 3a. Longifolene (CID 1796220), 3b. Diallyldisulphide (CID16590), 3c. Tocotrienol (CID 9929901), 3d. Cocculin (CID 6473767), 3e. Tangeretin (CID 68077), 3f. Camphene (CID 6616), 3g. Sulphoraphane (CID 336944062), 3h. Limonene (CID 22311), 3i. P. Cymene (CID 7463), 3j. Thymohydroquinone (CID 95779), 3k. Allylpropyldisulphide (CID 16591), 3l. Zingiberene (CID 92776), 3m. Flavone (CID 10680), 3n. Dithymoquinone (CID 398941), 3o. Gingerol (CID 442793)

Table 2: Names of compounds along with PubChem CIDs and number of violations of RO5

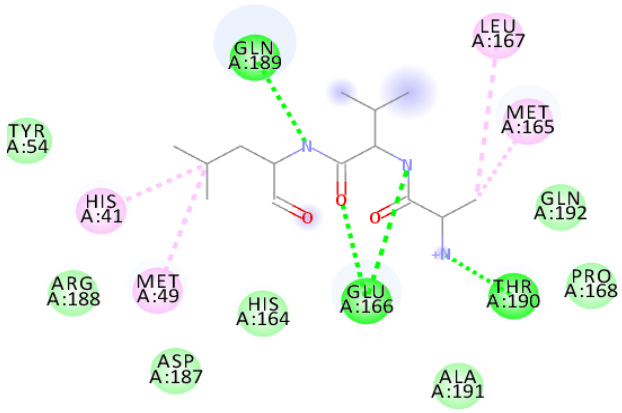
SL. No.	Drug/Herbal Compound	PubChem CID of Drug	Number of Violations of Drug
1.	Diallyldisulphide	16590	0
2.	Tocotrienol	9929901	1
3.	Longifolene	1796220	0
4.	Cocculin	6473767	0
5.	Tangeretin	68077	0
6.	Camphene	6616	0
7.	Sulphoraphane	336944062	-
8.	Limonene	22311	0
9.	P. Cymene	7463	0
10.	Thymohydroquinone	95779	0
11.	Allylpropyldisulphide	16591	0
12.	Zingiberene	92776	1
13.	Flavone	10680	0
14.	Dithymoquinone	398941	0
15.	Gingerol	442793	0

Table 3: Molecular properties of compounds

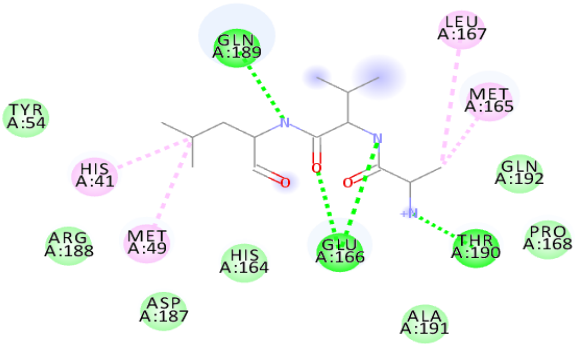
S. No.	compounds	miLogP	MW	nON	nOHNH
1.	Diallyldisulphide	2.63	146.28	0	0
2.	Tocotrienol	8.46	382.59	2	1
3.	Longifolene	4.95	204.36	0	0
4.	Cocculin	- 2.23	310.30	7	2
5.	Tangeretin	3.78	372.37	7	0
6.	Camphene	3.33	136.24	0	0
7.	Sulphoraphane	-	-	-	-
8.	Limonene	3.62	136.24	0	0
9.	P. Cymene	3.90	134.22	0	0
10.	Thymohydroquinone	3.26	166.22	2	2
11.	Allylpropyldisulphide	2.86	148.30	0	0
12.	Zingiberene	5.12	204.36	0	0
13.	Flavone	3.74	222.24	2	0
14.	Dithymoquinone	1.70	328.41	4	0
15.	Gingerol	3.22	294.39	4	2



4a.



4b.



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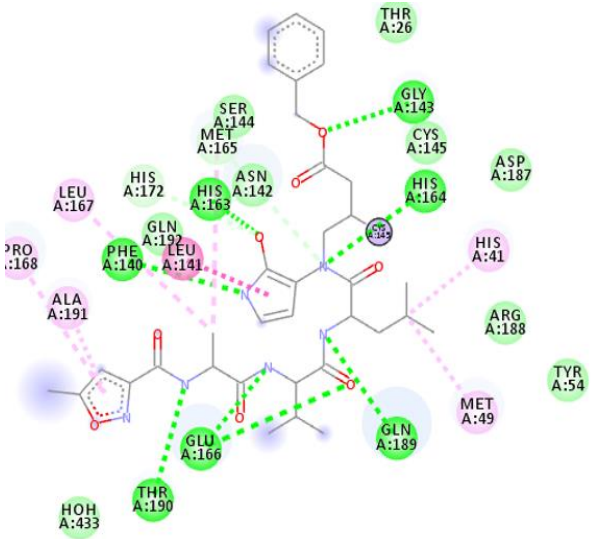

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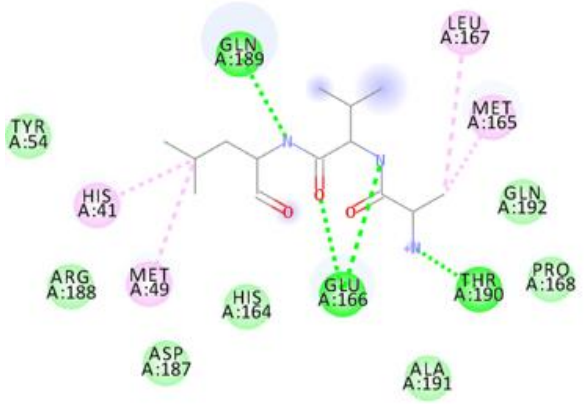

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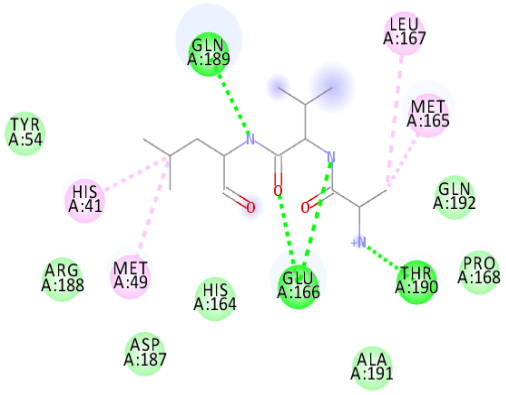

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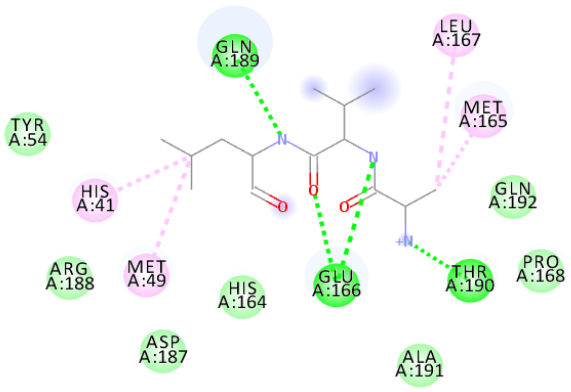

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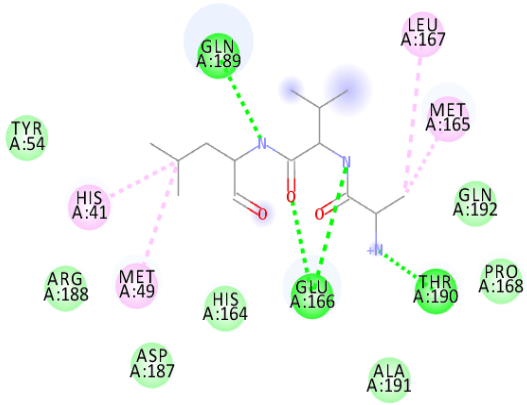

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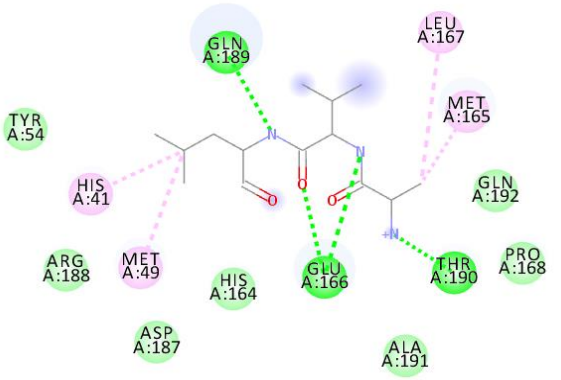

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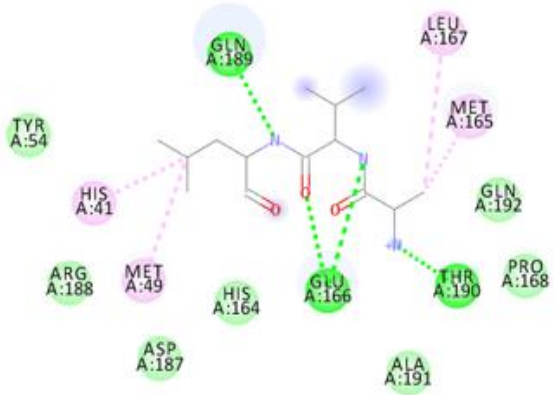

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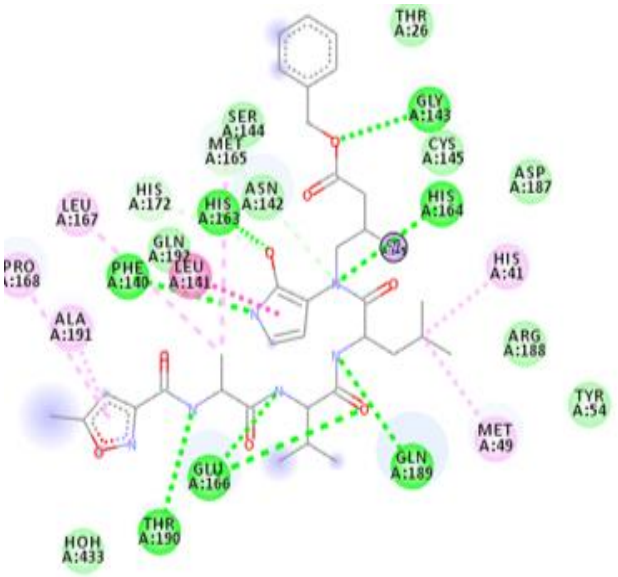

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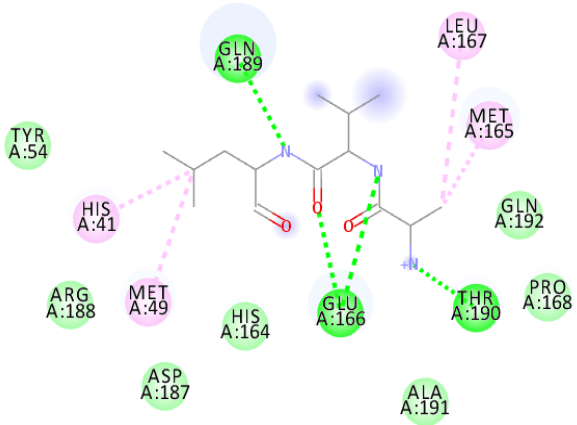

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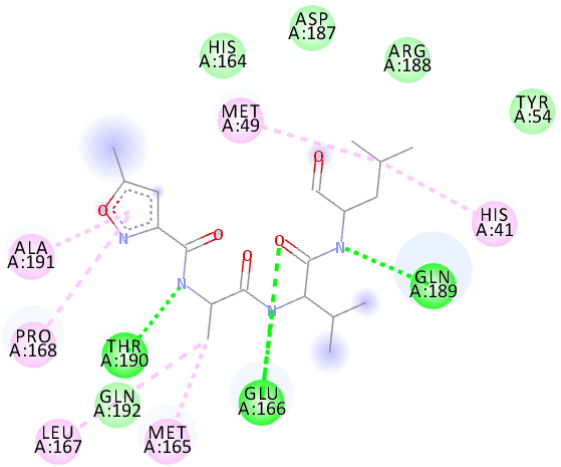

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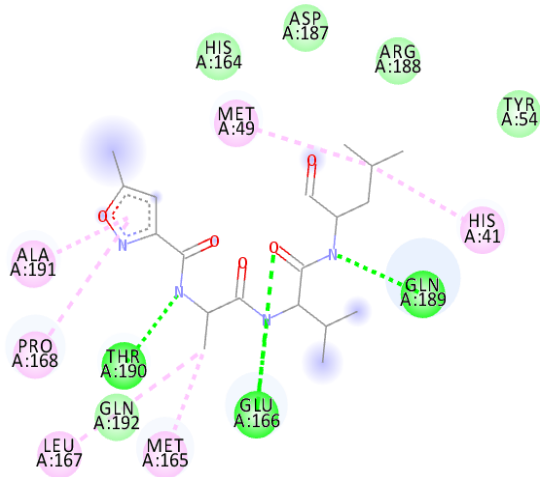

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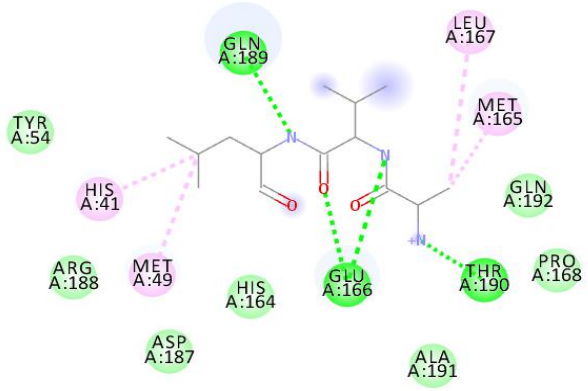

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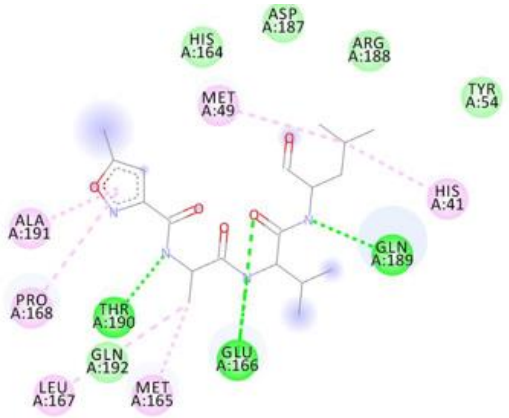

4p.

Figure 4: Docking results of following compounds-4a. hydroxychloroquine, 4b. Longifolene (CID 1796220), 4c. Diallyldisulphide (CID16590), 4d. Tocotrienol (CID 9929901), 4e. Cocculin (CID 6473767), 4f. Tangeretin (CID 68077), 4g. Camphene (CID 6616), 4h. Sulphoraphane (CID 336944062), 4i. Limonene (CID 22311), 4j. P. Cymene (CID 7463), 4k. Thymohydroquinone (CID 95779), 4l. Allylpropyldisulphide (CID 16591), 4m. Zingiberene (CID

92776), 4n. Flavone (CID 10680), 4o. Dithymoquinone (CID 398941), 4p. Gingerol (CID 442793)

4. Conclusion

In this work, we looked into the possibility of using longifolene and thymohydroquinone instead of hydroxychloroquine to treat COVID-19 and malaria. According to our in-silico docking research, protein 6LU7, which is essential for the effectiveness of antiviral and antimalarial medications, has binding sites that both phytochemicals share. Additionally, both traditional hydrogen bonds (HIS-163, PHE-140, GLY-143, HIS-164, GLN-189, GLU-166, THR-190) and Alkyl/pi-Alkyl bonds (LEU-167, PRO-168, ALA-191, MET-49, HIS-41) have been identified in the bonding interactions between these phytochemicals and 6LU7, which may help to form a stable and specific binding complex. These results imply that longifolene and thymohydroquinone should be studied more as possible COVID-19 and malaria treatment drugs.

5. Discussions

The emergence of resistance and possible negative effects are two issues facing the present antimalarial and antiviral medication repertory. To address these issues, it is essential to identify novel therapeutic medicines with unique modes of action. A valuable source for drug discovery efforts is natural products, especially phytochemicals, which have a long history of usage in traditional medicine [11]. By investigating the possibilities of longifolene and thymohydroquinone as hydroxychloroquine substitutes, this work adds to the continuing endeavor.

Our in-silico docking study offers encouraging preliminary data on these phytochemicals' potential. It is especially encouraging to find common binding sites for hydroxychloroquine on protein 6LU7, since this protein is essential to the life cycles of some coronaviruses and the malaria parasite Plasmodium spp. [12]. The possibility for stable and specific binding is suggested by the observed bonding interactions, which include conventional hydrogen bonds and Alkyl/pi-Alkyl bonds [13] [14].

It is critical to recognize the study's limitations. While in vivo safety and efficacy cannot be absolutely predicted, in-silico docking study offers insightful information. To assess the effectiveness of longifolene and thymohydroquinone against COVID-19 and malaria using in vitro and in vivo models, more research is required. Furthermore, research is necessary to evaluate the safety profile and possible adverse effects of these phytochemicals.

Overall, this study shows that longifolene and thymohydroquinone are viable substitutes for hydroxychloroquine in the management of COVID-19 and malaria. To confirm these results and investigate the potential therapeutic applications of these phytochemicals, more in vitro and in vivo studies are necessary.

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