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In silico Screening of Natural Compounds from *Jatropha curcas* (*Euphorbiaceae, Linn*) and *Jatropha gossypiifolia* (*Euphorbiaceae, Linn*) against SARS-CoV2 Targeting Mpro

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Abstract

Mpro SARS-Cov2, the COVID-19 main protease is set to be a good target for potential inhibitors, especially from plants. 6LU7, the crystal structure of COVID-19 enzyme has been used for docking with natural compounds from *Jatropha curcas* and *Jatropha gossypifolia* to verify anti-COVID potentials of these two plants. The molecular docking was done using PyRx 0.8 while the Swiss ADME website server used for physicochemical properties and PKCSM tool was used for pharmacokinetic properties prediction. The following compounds identified within *J. curcas* have given good binding affinities than Azithromycin (positive control): 2-methyl anthraquinone, Curcusone D, Palmarumycin CP1, Apigenin, Jatropholone A, Jatropholone B, Spirocurcasone and Multidione. The best binding score is for Palmarumycin CP1 -8.2 Kcal/mol with a gap sample of 0.28. All these compounds have satisfied Lipinski rules, have good Human Intestinal Absorption scores, and have good pharmacokinetic properties. In *J. gossypifolia*, 2,24,25-Trihydroxylanosta-1,7-dien-3-one; -Cleomiscosin A, Citlalitrione, Gossypifan, Jatrophenone, Jatropholone A, Jatropholone B, Gadain, Gossypidien, Falodone, and Gossypiline are having good binding affinities than Azithromycin (positive control). The best score is for Cleomiscosin A -8.2 Kcal/mol. All these compounds have satisfied Lipinski rules, have good Human Intestinal Absorption scores, and have good pharmacokinetic properties. This study has confirmed the anti-COVID-19 potential of these two plants.

Keywords: SARS-Cov2, Molecular docking, Jatropha curcas, Jatropha gossypiifolia, antiviral properties

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INTRODUCTION

Nowadays, the world leans to live under pressure from the current pandemic of COVID-19. This health crisis started in December 2019 in China and has been spread on a global scale concerning all layers of the community. It was reported that more than 6 million people died of this outbreak, which has also inflicted political and socioeconomic disruptions in our daily lives [1-2]. With no clinically approved drugs, the global health system is struggling to find an effective treatment measure. To deal with this crucial juncture, screening plant-derived compounds may be an effective strategy to fight against COVID-19 [3].

Despite the availability of vaccines, a survey showed that resistance to take these vaccines was due to their unknown composition and cost [4-5]. In most African cities, the healthcare facilities are located in urban areas while in rural areas; the population relies on herbs or traditional medicine to treat diseases and infections [4]. In parallel, the World Health Organization (WHO) recognizes that traditional and complementary medicines are a vital part of the global health care system. In Africa, it is estimated that over

80% of the population relies on medicinal plant species to meet their basic health care needs. The Democratic Republic of the Congo (DRC) is one of the most plant diversity-rich countries in Africa and contains 47% plant diversity of the African rainforest [6]. Therefore, a breeding ground for medicinal plants has several virtues.

Several studies have been carried out on natural compounds to find molecules or complexes, which display anti-COVID-19 properties by using the molecular docking method. In the search of finding potential inhibitors using molecular docking, a particular emphasis is on the meaning of the binding affinity of ligand-protein complexes and their drug-likeness properties [7-8].

Jatropha genus with 175 species belongs to the Euphorbiaceae family and it is reported for its diverse medicinal benefits [9-12]. Originating from Tropical America, *Jatropha* can be found over the tropics and subtropics of Asia and Africa. Its species are known to be important sources of secondary metabolites having a large spectrum of biological activities. [11]. In this research, our main focus was on two species of *Jatropha*, of which: *Jatropha curcas* and *Jatropha gossypifolia*. These species have been reported to have many pharmacological properties such as anti-HIV, antimicrobial, anti-cancer, anti-inflammatory, and antiviral [13-20].

COVID-19 disease is caused by infection with SARS-CoV-2 and 6LU7 is the PDB ID of the crystal structure of COVID-19 main protease [21-22]. Natural components identified through phytochemistry literature of *J. curcas* [23-27] and *J. gossypifolia* [28,29] have been docked against 6LU7.

MATERIALS AND METHODS

Protein preparation

The crystal structure of Mpro of SARS-CoV2 (PDB ID: 6LU7) from the protein data bank and imported in Discovery Studio. Secondly, hetero atoms and water molecules were removed from the structure**.** Finally, the binding site has been automatically determined and visualized.

ADME and ADMET profiling

After ligands structure were downloaded in SD format, isomeric smiles of each compound have been used for ADME (physicochemical properties) using SWISS ADME and ADMET (pharmacokinetic properties) using PKCSM. Azythromycin (Pubchem Id: 53477736), approved by the FDA (U.S. Food and Drug Administration) as an antibiotic and commonly used against COVID-19, has been used as control sample. The screening strategy of each is shown in the results.

RESULTS AND DISCUSSION

Jatropha curcas

a. Screening strategy

From the literature [23-27], we have noted 84 compounds that were identified within *J. curcas*. Passing through various processes.

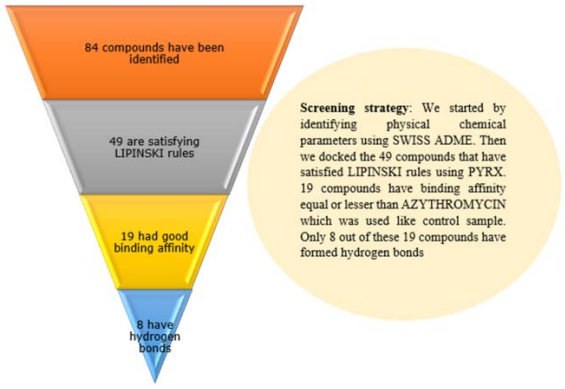


Figure 1. Screening strategy used for *J. curcas*

The above scheme illustrates the strategy that has been adopted in this research.

b. Binding affinities and hydrogen bonds

After molecular docking was performed using PYRX, aggregated complex and macromolecule have been visualized on Discovery studio.

The binding affinity and H-bonds of our compounds is presented in the **Table** 1. We can observe that Azithromycin PubChem CID 447043 has a binding affinity of -6.7 kcal/mol with a sample gap of 0.80. For the remaining, we can notice that the lowest energy is from Palmarumycin CP1, of which value is -8.2 kcal/mol with a sample gap of 0.28, and the highest is -6.8 kcal/mol with a sample gap of 0.19 from Multidione. All the eight compounds have less binding affinity than the control.

All the eight compounds have created hydrogen bonds. It was observed that Spirocurcasone, Multidione, and Jatropholone have respectively 4-3-2 hydrogen bonds while all the remaining have only a single H-bond. For all H-bonds, the distances are lower or equal to the sum of Van der Waals radii. It should be noted that we have 2 types of H-bonds, namely H=O and O=H.

Following substrates have been identified on H-bonds that have been performed: GLN A:110, GLU A: 166, SER A:144, LEU A:141, THR A:199, CYS A: 45, GLY A: 143, and CYS A: 145.

c. Physico-chemical parameters

These predicted results have been obtained using SWISS ADME (**Table** 2). The recommended range/value has been set referring to [29-31].

Table 1. Binding Affinity and H-Bonds

Compounds	Binding affinity kcal/mol	Hydrogen bonds				
		Count	Substrate	Type	Distance in Å	Sum of Van der Waals radii in Å
2-methyl anthraquinone	-7.3±0.20	1	GLN A:110	O=H	2.3	2.75
Curcusone D	-7.0±0.43	1	GLU A:166	O=H	1.82	2.75
Palmarumycin CP1	-8.2±0.28	1	SER A:144	O=H	2.41	2.75
Azithromycin	-6.7±0.80	Control sample				
Apigenin	-7.8±0.11	1	LEU A:141	H=O	2.48	2.75
Jatropholone A	-7.2±0.52	1	GLU A:166	H=O	2.46	2.75
Jatropholone B	-7.7±0.43	2	THR A:199	H=O	2.55	2.75
			GLN A: 110	O=H	2.52	2.75
Spirocurcasone	-7.4±0.78	4	CYS A:45	H=O	2.01	2.75
			SER A:144	H=O	1.97	2.75
			GLY A:143	H=O	2.73	2.75
			GLY A:143	H=O	2.75	2.75
Multidione	-6.8±0.19	3	SER A:144	H=O	2.29	2.75
			CYS A:145	H=O	2.49	2.75
			CYS A:145	H=O	2.5	2.75

Table 2. ADME Results

Parameters	Predicted results								Recommended range / value
	C1	C2	C3	C4	C5	C6	C7	C8	
Molecular weight (Da)	316.31	312.40	222.24	270.24	296.40	296.40	296.40	316.43	130–725
Molar refractivity	88.82	91.62	64.72	73.99	90.70	90.70	90.16	94.33	60-110
PSA	55.76	54.37	34.14	90.90	37.30	37.30	34.14	54.37	less than 140
Donor H-bond	1	1	0	3	1	1	0	1	0–6
Acceptor H-bond	4	3	2	5	2	2	2	3	2–20
Log P	3.92	3.31	2.77	2.57	4.62	4.62	4.19	4.55	-2–6.5

Legend: C1: Palmarumycin CP1
C2: Curcusone D
C3: 2-methyl anthraquinone
C4: Apigenin
Log P: Lipophilicity
C5: Jatropholone A
C6: Jatropholone B
C7: Spirocurcasone
C8: Multidione
PSA: Polar Surface Area

From **Table** 2, we can observe that none of the eight compounds have values higher than the recommended considering the six parameters that we have chosen. For the molecular weight, the lowest value is 222.24 for 2-methyl anthraquinone and the highest is 316.43 for Multidione. The molar refractivity values start from 64.72 which is for 2-methyl anthraquinone to 94.33 for Multidione.

Log P which represents the lipophilicity, the values are between 2.57 for Apigenin and 4.62 for

Jatropholone A and B. The values of Donor H-bond (HDB) and Acceptor H-bond (AHB) are between 0 and 3 for HBD while for AHB values are between 2 and 5. Adding the above, we just noticed that all eight compounds are not violating the R05 rules.

d. ADME-T predictive results

The below predictive results have been obtained using http://biosig.unimelb.edu.au/pkcsm/prediction after uploading of compounds smiles.

Table 3. ADME-T profile

	Parameters	C1	C2	C3	C4	C5	C6	C7	C8
Absorption & Distribution	BBB	0.162	0.213	0.398	-0.734	0.05	0.05	0.254	-0.161
	HIA	96.066	96.951	99.436	93.25	93.831	93.831	99.736	93.203
Metabolism	CYP2D6 substrate	No	No	No	No	No	No	No	No
	CYP3A4 substrate	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Excretion	Total Clearance	-0.073	1.167	0.211	0.566	0.561	0.561	-0.011	0.913
	Renal OCT2 substrate	No	Yes	No	No	No	No	Yes	No
Toxicity	Oral Rat Acute Toxicity (LD50)	2.275	1.73	2.11	2.45	2.179	2.179	1.728	2.148
	Hepatotoxicity	No	No	Yes	No	No	No	No	No

Legend:
C1: Palmarumycin CP1
C2: Curcasone D
C3: 2-methyl anthraquinone
C4: Apigenin
C5: Jatropholone A
C6: Jatropholone B
C7: Spirocurcasone
C8: Multidione

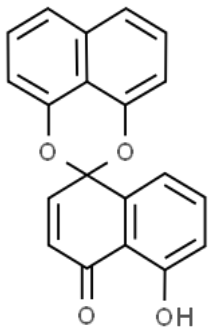
From **Table** 3, we notice that the two compounds notably Apigenin and Multidione have a Blood-brain barrier (BBB) permeability value less than 0, while the six remaining have positive values between 0.05 and for Jatropholone A and B to 0.398 for 2-methyl anthraquinone.

The human intestinal absorption rates of all eight compounds are above 30 as recommended. The minimum is 93.203 for Multidione while the maximum is 99.736 for Spiracurcasone. On the excretion side, we do notice that six out of eight compounds are no Renal OCT2 substrate. Thus, Palmarumycin CP1, 2-methyl anthraquinone, Apigenin, Jatropholone A and B, and Multidione can be eliminated through the OCT2 substrate. The values of total clearance of the eight compounds start from--0.073 ml/min/kg for Palmarumycin CP1 to 1.167 for Curcasone D. Regarding the toxicity, it was observed that only 2-methyl anthraquinone is hepatotoxic while the 7 remaining compounds are not.

e. Palmarumycin CP1 VS 6LU7

From the above results, in **Table** 1, we observed that Palmarumycin CP1 has the best binding affinity (-8.2 Kcal/mol) and having an interesting predictive result on SWISS ADME and ADME-T.

Palmarumycin CP1 (**Figure** 2) is one of the bioactive naphthalene diol spiroketals natural products. It has been reported as having antifungal, anti-bacterial, and anti-cancer bioactivity [31-32].



2D STRUCTURE

- Molecular Formula : $C_{20}H_{12}O_4$
- Molecular weight : 316
- PubMed CID : 196959

Figure 2. 2D structure of Palmarumycin CP1

In the **Figure** 3, the docking between Palmarumycin CP1 and 6LU7 is presented. It was observed in Figure 3 that the conventional H-bond is established on SER A:144 as the substrate (amino acid). The identification of H-bond type (in green) and

the ligand interaction distance is presented in the **Figure** 4.

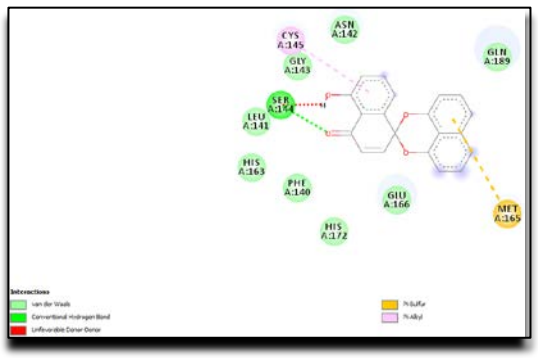


Figure 3. H-bonding interaction in 2D between Palmarumycin CP1 and 6LU7

Figure 4. H-bonding interaction in 3D Palmarumycin between CP1 and 6LU7

Jatropha gossipifolia

a. Screening strategy

From the literature [28-29], we have noted 36 compounds that were identified within *J. curcas*. Passing through various processes.

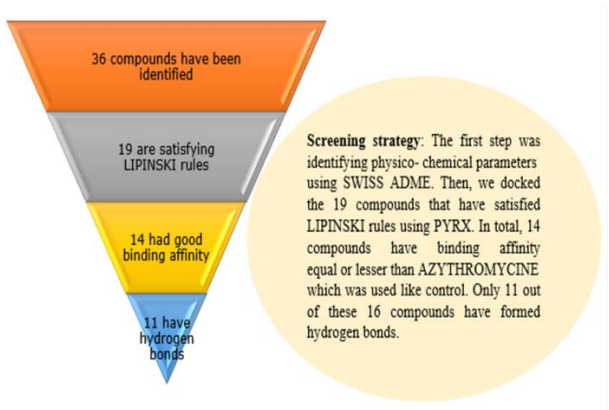


Figure 5. Screening strategy used for *J. gossypiifolia*

b. *Binding* affinities and hydrogen bonds

Having performed the molecular docking using PYRX, aggregated complex and macromolecule have been visualized on Discovery studio.

From **Table** 4, we can observe that Azithromycin PubChem CID 447043 has a binding affinity of -6.70 kcal/mol with a sample gap of 0.35. For the remaining, we can notice that the lowest energy is from Cleomiscosin A of which value is -8.2 kcal/mol with a sample gap of 0.39, and the highest is -6.70 kcal/mol with a sample gap of 0.39 from Gossipidien. However, 10 out of 11 compounds have less binding affinity than the control sample only Gossypidien has an equivalent binding affinity with Azithromycin.

All 11 compounds have created hydrogen bonds. Cleomiscosin A and 2,24,25-Trihydroxylanosta-1,7-dien-3-one have 3 hydrogen bonds; Jatrophenone, Jatropholone B, and Gossypidien have each 2 hydrogen bonds while all the remaining have only a single H-bond. Except for Jatrophenone which has an H-bond created through LYS A:102 with a distance higher than the SUM of Van der Waals radii in Å all H-bonds (2,90 > 2,75), all the distances are lower than the sum of Van der Waals radii. Mainly we do have 3 types of bonds H=O, O=H, and H-O.

c. Physico-chemical parameters

These predicted results have been obtained using SWISS ADME. The recommended range/value has been set referring to [29-31].

From **Table** 5, we can note that regarding the molecular weight (MW) all of the 11 compounds are in the recommended range. The lowest MW is for Falodone (289.39 while the highest is for 2,24,25-Trihydroxylanosta-1,7-dien-3-one (472.70).

On molar refractivity, two compounds have values higher than the recommended value: these are 2,24,25-Trihydroxylanosta-1,7-dien-3-one (139.60) and Gossypiline (114.17). For those who are in the recommended range, the lowest value is for Citlalitrione (90.53), and the highest value is for Gossypidien (104.88). The Polar Surface Areas of all 11 compounds are less than 140 Å. Thus, all of them are in the recommended range.

On H-bonds, all compounds are in the recommended range of acceptors and donors. On donors, the values of potential bonds are between 0 to 3 while on acceptors, the values of potential bonds are between 2 and 8. For Log P which represents the lipophilicity, the values are between 2.38 for Cleomiscosin A and 5.60 for 2,24,25-Trihydroxylanosta-1,7-dien-3-one. So these values are in the recommended range.

Adding to the above, we just noticed that all 11 compounds are not violating the R05 rules.

Table 4. Binding affinity and H-bonds

Compound	Binding affinity	Count	Substrate	Type	Distance	Sum of Van der Waals radii in Å
2,24,25-Trihydroxylanosta-1,7-dien-3-one	-7,37±0.39	3	THR A:111	H=O	2,32	2,75
			THR A:111	H=O	2,22	2,75
			ASN A:151	O=H	2,15	2,75
Cleomiscosin A	-8,2±0.39	3	GLY A:143	O=H	1,96	2,75
			GLY A:143	O=H	2,44	2,75
			LEU A:141	H=O	2,09	2,75
Citlalitrione	-7,53±0.45	1	GLN A:110	H=O	2,3	2,75
Azithromycin	-6,70±0.35	CONTROL SAMPLE				
Gossypifan	-6,80±0.15	1	THR A:199	H=O	2,06	2,75
Jatrophenone	-7,02±0.25	2	LYS A:102	H=O	2,9	2,75
			GLN A:110	H=O	2,32	2,75
Jatropholone A	-7,85±0.23	1	GLU A:166	H=O	2.46	2.75
Jatropholone B	-7,75±0.55	2	GLN A:110	H=O	2,08	2,75
			SER A:158	O=H	2,29	2,75
Gadain	-7,30±0.31	1	GLN A:110	H-O	2,25	2,75
Gossypidien	-6,70±0.63	2	GLY A:143	H-O	2,31	2,75
			GLU A:166	H-O	2,42	2,75
Falodone	-7,70±0.17	1	SER A:158	O=H	1,89	2,75
Gossypiline	-7,23±0.17	1	GLY A:143	H-O	2,04	2,75

Table 5. ADME Results

Parameters	Predicted results											Recommended range/value
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	
Molecular weight (Da)	472.70	440.44	368.38	386.35	410.37	296.40	296.40	330.42	284.39	352.34	358.47	130–725
Molar refractivity	139.60	114.17	98.47	98.82	104.88	90.70	90.70	90.53	85.41	91.54	103.90	60-110
PSA	77.76	89.52	63.22	107.59	89.52	37.30	37.30	63.74	37.30	63.22	60.44	less than 140
H-bond acceptors	4	8	6	8	8	2	2	4	2	6	4	2–20
H-bond donors	3	0	0	2	0	1	1	0	1	0	0	0–6
Log P	5.60	3.51	3.23	2.38	2.95	4.622	4.622	2.88	4.404	2.94	4.0631	-2–6.5

Legend: C1: 2,24,25-Trihydroxylanosta-1,7-dien-3-one C2: Gossypiline
C3: Gossypifan C4: Cleomiscosin A C5: Gossypidien
C6: Jatropholone A C7: Jatropholone B C8 : Citlalitrione
C9: Falodone C10: Gadain C11 : Jatrophenone
LOGP: Lipophilicity

d. ADME-T predictive results

The below predictive results have been obtained using http://biosig.unimelb.edu.au/pkcsm/prediction after uploading of compounds smiles. From table 6, we notice that 7 of the 11 compounds have a Blood-brain barrier (BBB) permeability value less than 0 starting from Jatrophenone -1.136 up to -0.219 for Gossypifan,

while the 4 remaining have positive values between 0.05 for Jatropholone A and B and 0.078 for Gadain. The human intestinal absorption rates of all 11 compounds are above 30 as recommended. The minimum is 87.493 for Gossypiline, while the maximum is 99.75 for Gossypifan. On the excretion side, we do notice that all 11 compounds are no Renal OCT2 substrate. Thus, all of them can be eliminated through the OCT2 substrate. The values of Total Clearance of the 11 compounds start from 0.191 ml/min/kg for Citlatrione to 0.968 for Gossipidien. It should be noted that none of the 11 compounds are hepatotoxic.

Table 6. ADME-T profile

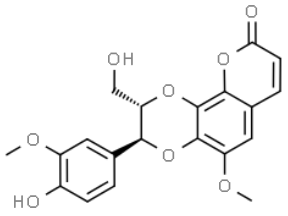
	Compound	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
Absorption & Distribution	BBB	-0.899	-0.48	-0.219	-0.748	0.117	0.05	0.05	-1.086	-1.064	0.078	-1.136
	HIA	96.253	87.493	99.75	96.478	98.072	93.831	93.831	98.785	99.277	94.079	97.699
Metabolism	CYP2D6 substrate	No	No	No	No	No	No	No	No	No	No	No
	CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Excretion	Total Clearance	0.446	0.394	0.485	0.393	0.968	0.561	0.561	0.191	0.347	0.556	0.271
	Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No	No
Toxicity	Oral Rat Acute Toxicity (LD50)	4.054	2.51	2.363	2.553	1.899	2.179	2.179	2.589	2.851	2.355	2.666
	Hepatotoxicity	Yes	No	No	No	No	No	No	No	No	No	No

C1: 2,24,25-Trihydroxylanosta-1,7-dien-3-one C2: Gossypiline
C3: Gossypifan C4: Cleomiscosin A C5: Gossypidien
C6: Jatropholone A C7: Jatropholone B C8: Citlalitrione
C9: Falodone C10: Gadain C11: Jatrophenone

e. Cleomiscosin A VS 6LU7

From the above results, we can see that Palmarumycin CP1 has the best binding affinity (-8.2 Kcal/mol), and we noticed interesting predictive results on SWISS ADME and ADME-T.

Cleomiscosin A (**Figure** 4) has been firstly isolated from the seeds of *Cleome viscosa*. It has been classified as coumarin-lignoid and its structure has been advanced based on physico-chemical evidence. It has been reported to have anti-inflammatory, anti-leukemic, and other anti-cancer bioactivities [34-35].



2D STRUCTURE

- Molecular Formula $C_{20}H_{18}O_8$
- Average mass386.352
- Pubmed Id: 442510

Figure 6. 2D structure of Cleomiscosin A

In **Figure** 7, we can see the docking between Clemiscosin A and 6LU7. it can be observed that the conventional H-bond is established on LEU A:144, CYS A:145, and GLY A: 143 as the substrates (amino acids).

In **Figure** 8, we can identify the type of H-bond (in green) and the ligand interaction distances.

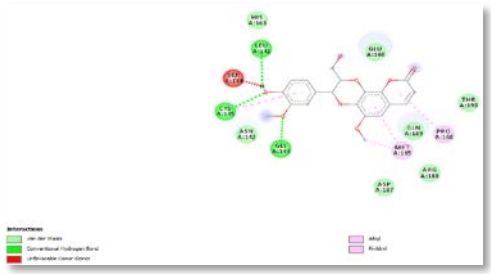


Figure 7. H-bonding interaction in 2D between Cleomiscosin A and 6LU7

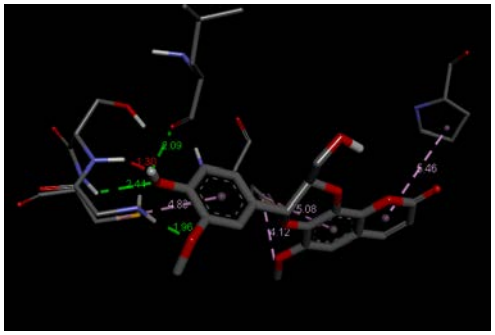


Figure 8. H-bonding interaction in 3D between Cleomiscosin A and 6LU7

CONCLUSION

Due to multiple factors, the world is continuing to face the resurgence of old diseases or in certain cases new ones. Some of them evolve into epidemics and then pandemics. This situation requires a proactive and reactive approach from researchers.

From this research, we noted that 8 of the chemical compounds isolated from *J. curcas* have a higher binding affinity with 6LU7 (the SARS-COV 2 main protease) than Azithromycin which is used currently to fight against COVID-19. With one or more hydrogen bonds and interesting physicochemical properties also adding ADME-T properties, these compounds could be considered good COVID-19 fighters.

J. gossypifolia also has 11 compounds that have a higher affinity with 6LU7 (the SARS-COV 2 main protease) than Azithromycin which is used currently to fight against COVID-19. The ADME and ADME-T results are also showing that these compounds could play an important role in the fight against COVID-19. Cleomiscosin A and Palmarumycin CP1 have shown the highest score of the two groups. According to the literature, we found particular pharmaceutical properties for these two groups.

We then suggest that more deep research regarding *J. curcas* and *J. gossypifolia* could be conducted on COVID-19, Hepatitis-B, and different cancers.

DECLARATION

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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