Prediction of Anti-COVID 19 Therapeutic Power of Medicinal Moroccan Plants Using Molecular Docking

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ABSTRACT: The emerging pathogen SARS-CoV2 causing coronavirus disease 2019 (COVID-19) is a global public health challenge. To the present day, COVID-19 had affected more than 40 million people worldwide. The exploration and the development of new bioactive compounds with cost-effective and specific anti-COVID 19 therapeutic power is the prime focus of the current medical research. Thus, the exploitation of the molecular docking technique has become essential in the discovery and development of new drugs, to better understand drug-target interactions in their original environment. This work consists of studying the binding affinity and the type of interactions, through molecular docking, between 54 compounds from Moroccan medicinal plants, dextran sulfate and heparin (compounds not derived from medicinal plants), and 3CLpro-SARS-CoV-2, ACE2, and the post fusion core of 2019-nCoV S2 subunit. The PDB files of the target proteins and prepared herbal compounds (ligands) were subjected for docking to AutoDock Vina using UCSF Chimera, which provides a list of potential complexes based on the criteria of form complementarity of the natural compound with their binding affinities. The results of molecular docking revealed that Taxol, Rutin, Genkwanine, and Luteolin-glucoside have a high affinity with ACE2 and 3CLpro. Therefore, these natural compounds can have 2 effects at once, inhibiting 3CLpro and preventing recognition between the virus and ACE2. These compounds may have a potential therapeutic effect against SARS-CoV2, and therefore natural anti-COVID-19 compounds.

KEYWORDS: Molecular docking, SARS-CoV2, anti-COVID 19, Moroccan plants

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Introduction

Emerging and re-emerging pathogens are global public health challenges.[1] Coronaviruses are non-segmented, enveloped, positive RNA viruses belonging to the family Coronaviridae and the order Nidovirales and are widely distributed in humans and other mammals.[2] The coronavirus of severe acute respiratory syndrome 2 (SARS-CoV-2), the most recently discovered, which causes COVID-19, has spread rapidly in China and other countries.[3-11] Thus, by October 20, 2020, COVID-19 had affected more than 40 million people worldwide.[12]

The development of novel, cost-effective, and specific anti-COVID 19 drugs is the prime focus of the current medical research.[13] The exploration of new bioactive compounds with anti-COVID 19 therapeutic power must target nature directly. Multiple scientific research works have revealed the enormous therapeutic antiviral potential of several medicinal plants and algae.[14,15] Indeed, infection by SARS-CoV 2 may be limited by different stratagems. One can consider blocking the entry of the virus into the host cell, by targeting either the spike protein S2 or the ACE2 protein of the plasma membrane to which the virus binds. However, another strategy would be to prevent the formation of viral RNA. Blocking the virus protease could prevent it from cutting the viral poly-protein synthesized by the infected cell. The viral particles could not assemble in the cell, which will stop the infection.[16-19]

In recent years, molecular modelling more precisely molecular docking has very quickly integrated the fields of biology, pharmacy, and medicine, seen its impact on improving efficiency and reducing the cost of research.[20,21] The increasing number of protein crystal structures, especially in the most popular public protein structure database: the database Protein Data Bank (PDB) shows the interest and development of research on molecular docking.[22] Also, the public databases such as DrugBank,[23] ChEMBL,[24] ZINC,[25] and PubChem[26] give the public the opportunity of accessing the structures and biological activities of millions of chemical compounds. Molecular docking has become an indispensable technique and has begun to have an impact on drug discovery and development, by studying drug-target interactions in their native environments.[27]

The objective of our work is the use of bioinformatics tool 'Molecular Docking', which anchors small molecules in the target structures of macromolecules and note potential complementarity with the binding sites to identify the drugs hits and optimize therapeutic leads. Thus, the molecular docking of natural molecules derived medicinal plants could be a therapeutic alternative to fight the SARS-CoV2.

Materials and Methods

To meet our goal, we have adopted the molecular docking approach. This approach consists of studying the binding affinity and the type of interactions, between 54 compounds from Moroccan medicinal plants (ligands) and the 3 key proteins involved in SARS-CoV2 infection: 3CL protease (3CLpro)-SARS-CoV-2, human angiotensin-converting enzyme (ACE2), and the post-fusion core of 2019-nCoV S2 subunit (receptors).

Data collection

We selected several plants from the Moroccan flora used in traditional medicine. These plants are known for their antimicrobial and anti-cancer power. The list is obtained by consulting several scientific publications.[28-33] Regarding heparin and dextran sulfate (compounds not derived from medicinal plants), their antiviral activity has already been proven in the literature, and can thus be proposed as an anti-COVID 19 molecule.[34,35] In total, we have listed 54 compounds from different medicinal plants and heparin and dextran sulfate (Table 1). The PubChem database[26] was consulted to assign each compound its ID and retrieve their chemical structure.

Molecular docking

The crystal structure of the human ACE2 (ID: 1R4L), 3CLpro-SARS-CoV-2 (ID: 6M2N), and the post-fusion core of 2019-nCoV S2 subunit (ID: 6LXT) was recovered by the PDB RCSB database.[22] Ligands and ACE2, 3CLpro-SARS-CoV-2, and spike protein S2 were prepared for docking using UCSF Chimera.[36] The steps for preparing ligands and proteins for docking protocol were done employing default settings. Afterwards, the PDB files of the target proteins and prepared compounds (ligands) were subjected to AutoDock Vina[37] to predict the structure of the protein-ligand complexes and to evaluate the binding energy. To predict the ideal mode of binding between the target proteins (IDs: 1R4L, 6M2N, and 6LXT) and each compound shown in Table 1, the results of molecular docking are analysed using Discovery Studio 2020.[38]

Results and Discussion

In this study, the molecular docking analysis was used to identify the anti-COVID-19 potential of natural compounds, derived from medicinal plants, and other synthetics molecules such as dextran sulfate and heparin.

In the docking analysis, chemical compounds and the structure of ACE2, 3CLpro, and spike protein S2 were submitted to AutoDock Vina, which provides a list of potential complexes based on the criteria of form complementarity of the chemical compound with their binding affinities. The binding affinity values of docked natural compound-protein complex were calculated according to the binding affinity energies.

ACE2-ligands docking analysis

The human ACE2 structure of SARS-CoV-2 recovered by the RCSB PDB server with the pdb identifier 1R4L revealed that the ACE2 has a resolution of 3.00 Å, a total structural weight 76.98 kDa and a residue number 655.

The ACE2-ligands docking analysis revealed that among the 56 chemical compounds tested (Table 1), 14 have a low binding energy and therefore a good interaction with ACE2 (Table 2). The compounds Taxol, Rutin, Baccatin III, Genkwanine, Ursolic acid, Luteolin-glucoside, and Alpha-Amyrin have the lowest binding energies (Table 2). Taxol has the lowest binding energy (equal to −12.2 Kcal/mol) (Figure 1, Table 2). The Rutin has a value of −11.4 Kcal/mol with 3 hydrogen bonds ALA 348, GLU 375, and GLU 402 (Table 2). Baccatin III has a value of −11.3 Kcal/mol and a hydrogen bond with ASP 368 (Table 2).

These compounds can bind directly to the ACE2 receptor with high affinity which may suggest for competition with SARS-CoV-2. Thus, this strategy turns out to be difficult to implement because the receptor in question is necessary for other vital cellular functions.[39,40]

Spike protein S2-ligands docking analysis

The post-fusion core of 2019-nCoV S2 subunit structure of SARS-CoV-2 recovered by the RCSB PDB server with the pdb identifier 6LXT revealed that the spike protein S2 has a resolution of 2.90 Å, a total structural weight 84.66 kDa, and a residue number 686.

The spike protein S2-ligands molecular docking analysis revealed that the chemicals compounds tested (Table 1) have high binding energy scores. Genkwanine has binding energy equal to −5.0 Kcal/mol, and two hydrogen bonds with ARG 1185. Rosmanol (equal to −4.8 Kcal/mol) has a hydrogen bond with LYS 1181 (Table 2). These values of binding energies (Table 2) reflect the instability of the interactions between the site of inhibition of spike protein S2 and the ligands tested (Table 1). These results suggest that the natural compounds tested (Table 1) do not have a strong affinity with the spike protein and are therefore unable to hinder the entry of SARS-CoV2 to the host cell.

However, despite the weak interactions of heparin with the spike protein S2 inhibition site (−3.4 Kcal/mol), heparin showed a high affinity (−8.0 Kcal/mol) with the protein outside the site of inhibition (data not shown). Therefore, this molecule can inhibit SARS-CoV-2 either by changing the three-dimensional structure of spike protein S2 or else hiding the active site of the latter. These results are consistent with the study of Kwon et al,[41] which showed that heparin effectively inhibits SARS-CoV-2 in vitro.

3CLpro-ligands docking analysis

The 3CLpro structure of SARS-CoV-2 recovered by the RCSB PDB server with the pdb identifier 6M2N revealed that

Table 1. List of 54 compounds from different medicinal plants and 2 synthetic compounds.

PUBCHEM CID	NAME	PLANT
3084656	Dextran sulfate[a]	–
772	Heparin[a]	–
5280450	Linoleic acid	*Marrubium vulgare*
11601669	CBDV	*Cannabis sativa* L.
16078	THC	*Cannabis sativa* L.
644019	CBD	*Cannabis sativa* L.
14986	Tocopherols	*Argania spinosa L.*
11027	3-Thujanone	*Artemisia herba-alba*
2537	Camphor	*Artemisia herba-alba*
88556	Davanone D	*Artemisia herba-alba*
442463	Chrysanthenone	*Artemisia herba-alba*
520909	α-Himachalene	*Cedrus atlantica* Mannerti
577062	γ-Himachalene	*Cedrus atlantica* Mannerti
11586487	β-Himachalene	*Cedrus atlantica* Mannerti
91698329	γ-Atlantone	*Cedrus atlantica* Mannerti
2758	1,8-Cineole	*Laurus nobilis & Laurus azorica*
6549	Linalool	*Laurus nobilis & Laurus azorica*
111037	α-Terpinyl acetate	*Laurus nobilis & Laurus azorica*
5280445	Luteolin	*Rosmarinus officinalis L.*
5280443	Apigenin	*Rosmarinus officinalis L.*
5281612	Diosmetin	*Rosmarinus officinalis L.*
5281628	Hispidulin	*Rosmarinus officinalis L.*
161271	Salvigenin	*Rosmarinus officinalis L.*
442018	Genkwanine	*Rosmarinus officinalis L.*
339816	Diterpene II (lactone)	*Rosmarinus officinalis L.*
5281792	Rosmarinic acid	*Rosmarinus officinalis L.*
1794427	Chlorogenic acid	*Rosmarinus officinalis L.*
13966122	Rosmanol	*Rosmarinus officinalis L.*
15801061	Rosmadial	*Rosmarinus officinalis L.*
442009	Carnosol	*Rosmarinus officinalis L.*
73170	Alpha-Amyrin	*Rosmarinus officinalis L.*
64945	Ursolic acid	*Rosmarinus officinalis L.*
10494	Oleanolic acid	*Rosmarinus officinalis L.*
222284	β-Sitosterol	*Taxus baccata L.*
44351600	11-Taxadiene	*Taxus baccata L.*
167825	Taxusin	*Taxus baccata L.*

(Continued)

Table 1. (Continued)

PUBCHEM CID	NAME	PLANT
15378021	Baccatin VI	*Taxus baccata L.*
65366	Baccatin III	*Taxus baccata L.*
5318150	Hydroxybaccatin I	*Taxus baccata L.*
36314	Taxol	*Taxus baccata L.*
442495	Pulegone	*Satureja calamintha spp. nepeta*
6986	Isomenthone	*Satureja calamintha spp. nepeta*
22311	Limonene	*Satureja calamintha spp. nepeta*
9064	Catechin	*Satureja*
21550	Caffeine	*Satureja*
5280805	Rutin	*Satureja*
72378	Lycorine	*Satureja*
10364	Carvacrol	*Satureja*
7461	γ-Terpinene	*Satureja*
6989	Thymol	*Satureja*
7463	p-Cymene	*Satureja*
445858	Ferulic acid	*Satureja*
338	Salicylic acid	*Satureja*
370	Gallic acid	*Satureja*
72276	Epicatechin	*Satureja*
5280637	Luteolin-glucoside	*Satureja*

[a]Dextran sulfate and heparin are compounds not derived from medicinal plants.

Table 2. List of natural compounds with the lowest binding energy and their hydrogen bond interactions with ACE2, the post fusion core of 2019-nCoV S2 subunit, and 3CLpro.

	NAME	H BONDS	BINDING ENERGY (KCAL/MOL)
ACE2-ligands	Taxol	0	**–12.2**
	Rutin	ALA 348, GLU 375, GLU 402	**–11.4**
	Baccatin III	ASP 368	**–11.3**
	Genkwanine	0	**–10.5**
	Ursolic acid	0	**–10.5**
	Luteolin-glucoside	ASP 368	**–10.2**
	Alpha-amyrin	0	**–10.2**
	Rosmanol	0	–9.9
	β-Sitosterol	0	–9.8
	Oleanolic acid	THR 371	–9.2
	Carnosol	0	–9.2
	THC	0	–9.2
	Hispidulin	TYR 515	–9.0
	Diterpene II (lactone)	0	–9.0

(Continued)

Table 2. (Continued)

	NAME	H BONDS	BINDING ENERGY (KCAL/MOL)
Spike protein S2-ligands	Genkwanine	2× ARG 1185A	–5.0
	Rosmanol	LYS 1181A	–4.8
	Luteolin-glucoside	GLU 1188A	–4.5
	Rosmarinic acid	0	–4.5
	Oleanolic acid	GLU 1188A	–4.4
	Rutin	ASP 1184A	–4.4
	Diterpene II (lactone)	0	–4.4
	Alpha-amyrin	0	–4.4
	Carnosol	0	–4.3
	Ursolic acid	0	–4.3
	THC	0	–4.2
	Chlorogenic acid	ARG 1185A	–4.0
3CLpro-ligands	Genkwanine	GLN 192A	**–8.5**
	Luteolin-glucoside	3 H Bonds ASN 142A	**–8.4**
	Rutin	ASN 142A, HIS 164A, 2× GLU 166A	**–8.0**
	Luteolin	0	–7.8
	Diterpene II (lactone)	CYS 145A	–7.8
	Rosmarinic acid	LEU 141A, GLU 166A	–7.7
	Catechin	LEU 141A, CYS 145A	–7.5
	Taxol	ASN 142A, GLU 166A	–7.5
	Diosmetin	LEU 141A, CYS 145A	–7.4
	Hispidulin	0	–7.3
	Dextran sulfate	THR 26A, HIS 41A, GLY 143A, ASP 187A	–7.2
	Apigenin	0	–7.2
	Salvigenin	ASN 142A, GLN 192A	–7.2
	Chlorogenic acid	GLU 166A, CYS 145A, 2× THR 190A	–7.2

The values in bold correspond to molecules which have a high affinity with the receptor in question.

the 3CLpro-SARS-CoV-2 has a resolution of 2.20 Å, a total structural weight 136.38 kDa, and a residue number 1223.

The molecular docking analysis revealed that among the 56 chemical compounds tested, 17 have a low binding energy and therefore a good interaction with 3CLpro (Table 2). The compounds Genkwanin, Luteolin-glucoside, and Rutin have the lowest binding energies (Table 2). Genkwanin has the lowest binding energy (equal to –8.5 Kcal/mol) and a hydrogen bond with GLN 129 (Table 2), and interacts with the active site (His-41, Cys-145 catalytic dyad), essential residues for the activity of SARS-CoV-2 3CLpro (Figure 2).[42,43] Luteolin-glucoside has a value of –8.4 Kcal/mol and 3 hydrogen bonds with ASN 142 (Table 2). The Rutin has a value of –8.4 Kcal/mol and 4 hydrogen bonds ASN 142, HIS 164, and 2× GLU 166 (Table 2). Moreover, Luteolin-glucoside and Rutin interact only with His-41 of the catalytic dyad (Figures 3 and 4).

The lowest binding energies and the presence of hydrogen bonding interactions in our ligand 3CLpro complex show the existence of strong interactions between these 3 natural compounds and our target protein. However, inhibition of 3CLpro's activity is among the most important therapeutic targets against coronaviruses, since this enzyme is crucial during viral replication.[44,45] The enzyme's active site contains a catalytic dyad (His-41, Cys-145) where a cysteine residue acts as a

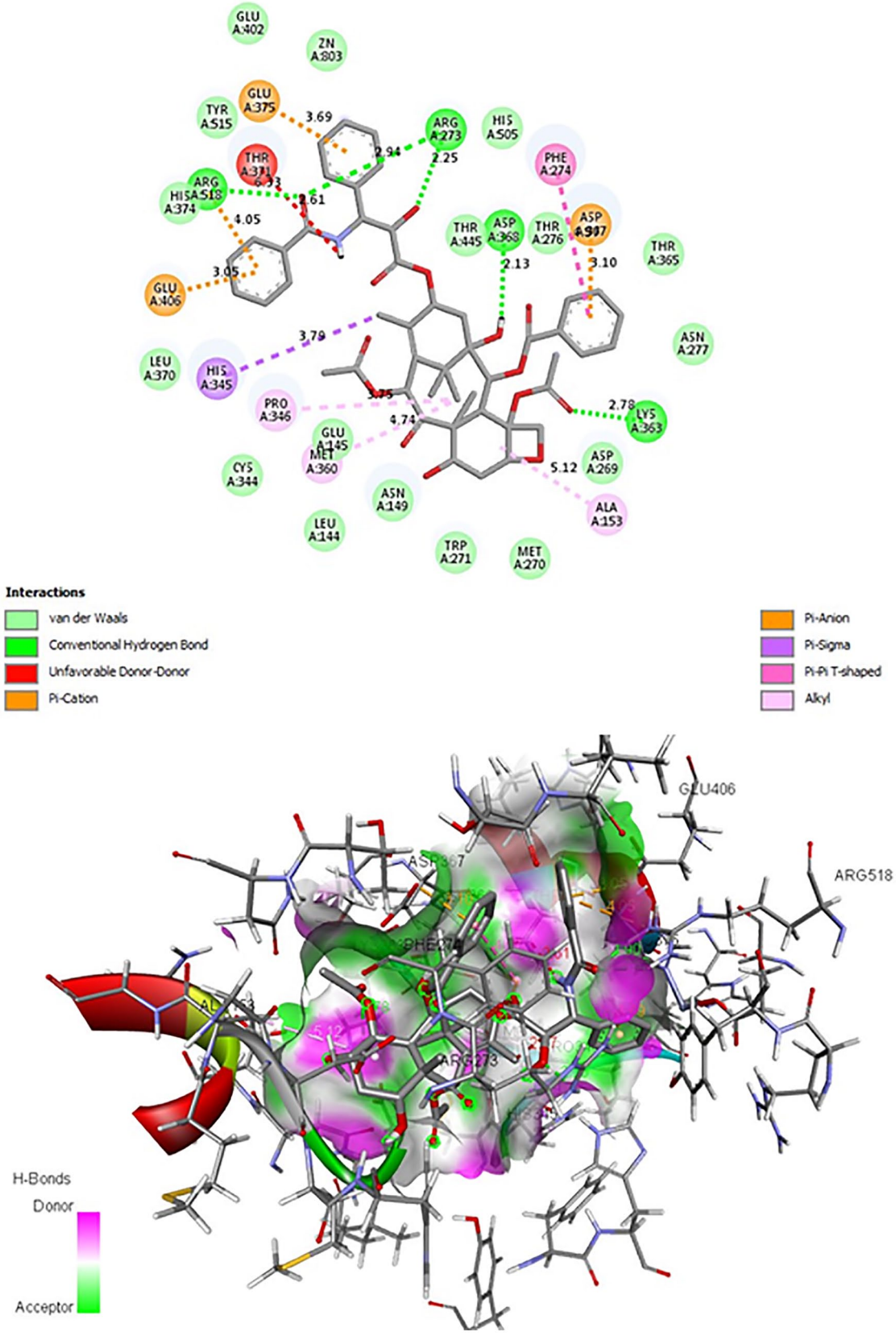

Figure 1. Interaction of the ligand Taxol with the active site of ACE2.

nucleophile in the proteolytic process and a histidine residue acts as the general acid base.[42,46-48] The molecular docking analysis revealed that Luteolin-glucoside and Rutin interact only with His-41 of the catalytic dyad (Figures 3 and 4). However, the Genkwanin can target 3CLpro through interactions regulating the catalytic dyad (Cys-145, His-41) of

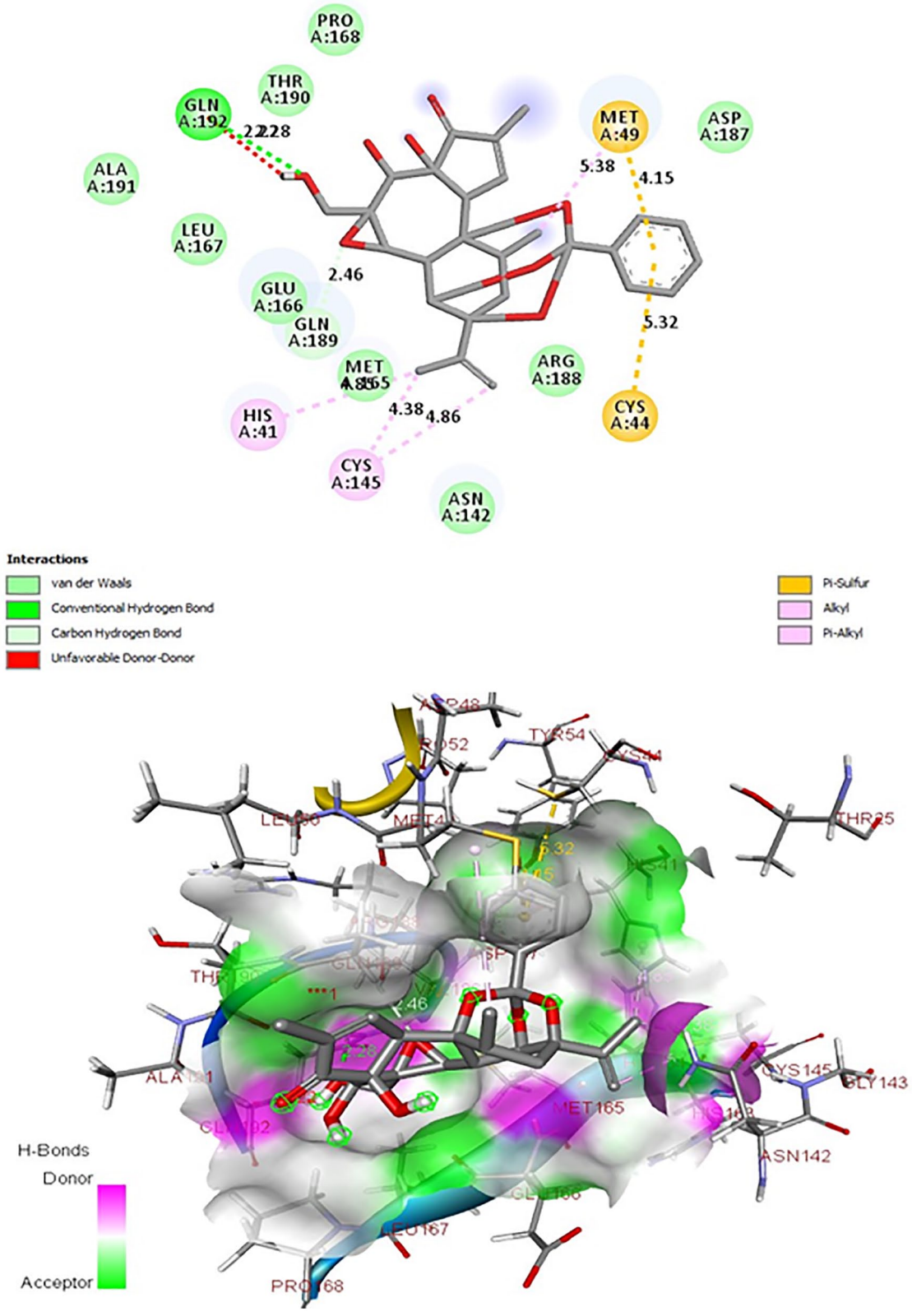

Figure 2. Interactions of the ligand Genkwanine with the active site of 3CLpro.

SARS-CoV-2 3CLpro (Figure 2), and in this sense, it is believed to hinder protease activity, and therefore natural anti-COVID-19 compound.

Taken together, the analysis of the molecular docking of the 2 membrane receptors (spike protein S2 and ACE2) as well as the viral protease 3CLpro revealed that the natural compounds

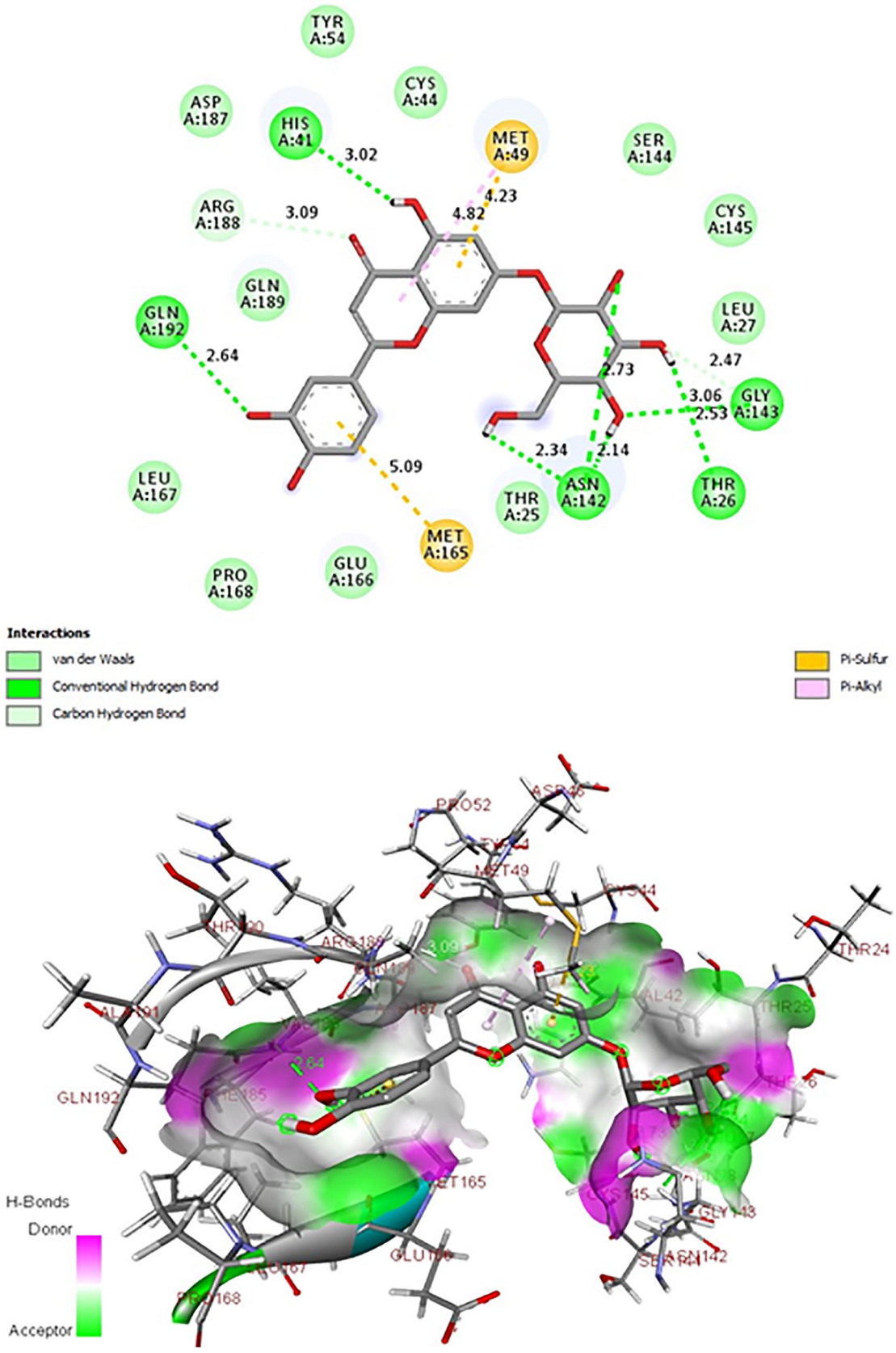

Figure 3. Interactions of the ligand Luteolin-glucoside with the active site of 3CLpro.

Taxol, Rutin, Baccatin III, Genkwanine, Ursolic acid, Luteolin-glucoside, and Alpha-Amyrin have strong affinities with ACE2, and therefore can be suggested for competition with SARS-CoV-2. The compounds Genkwanine, Luteolin-glucoside, and Rutin can be potential inhibitors of 3CLpro, and therefore natural anti-COVID-19 compounds. During

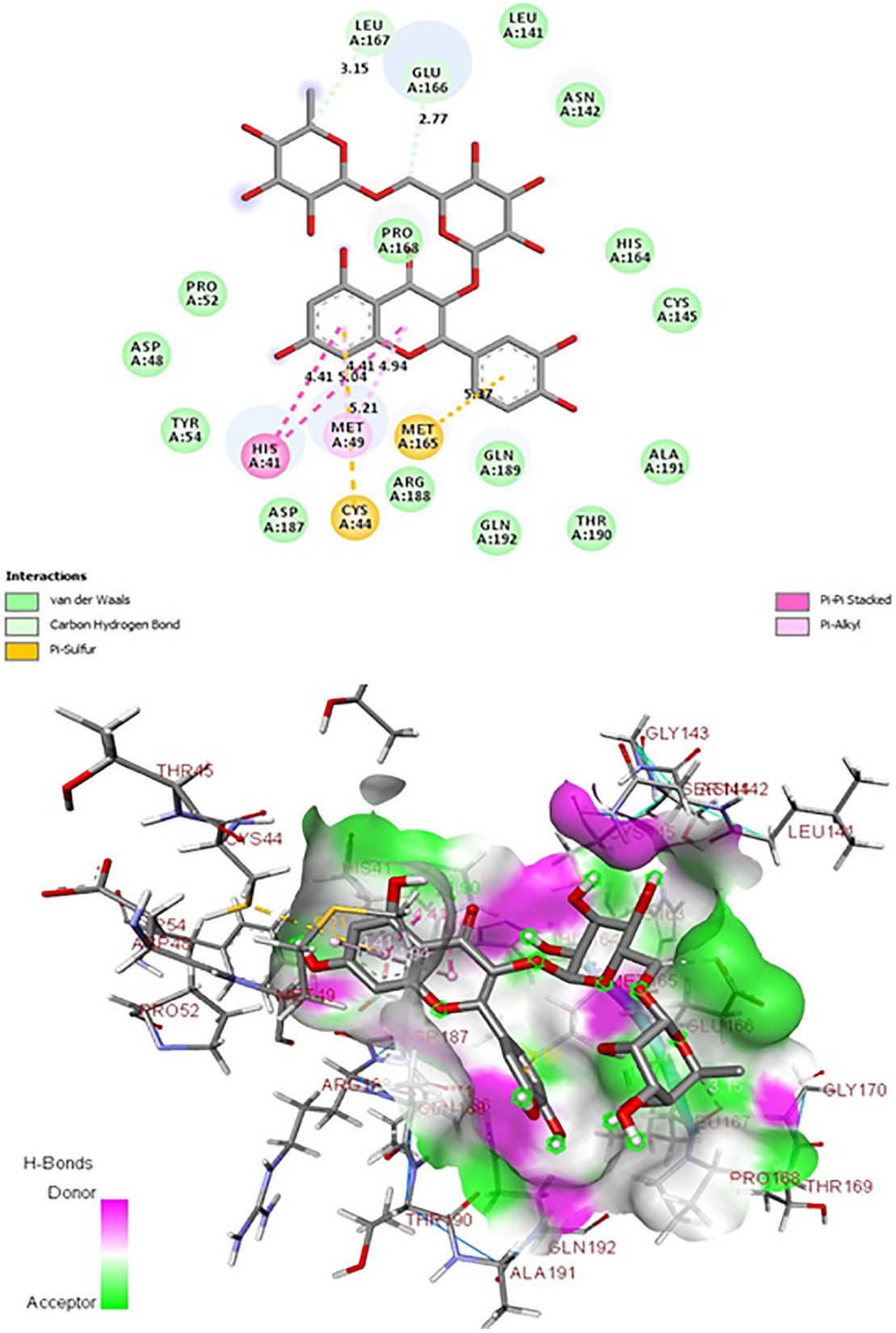

Figure 4. Interactions of the ligand Rutin with the active site of 3CLpro.

this study, the natural compounds listed in Table 1 showed high affinity to the therapeutic targets 3CLpro SARS-CoV2 and human ACE2, compared with dextran sulfate and heparin. However, the results of our study revealed that heparin has a potential to inhibit the function of the spike membrane receptor, compared with natural compounds (Table 1). These have

an unstable interaction with the spike protein, and therefore cannot hinder the entry of SARS-CoV2 into the host cell.

In our study, Taxol, Rutin, Genkwanine, and Luteolin-glucoside have high affinities with ACE2 and 3CLpro. These results agree with other experimental studies, showing the important antiviral power of these molecules of natural origin. Taxol (*Taxus baccata L.*) has been reported to have antiviral activity.[49,50] Thus, Taxol has the capacity to inhibit the entry of HIV-1 virus into cells. Moreover, this molecule not only acts on the process before the virus invades, but also has an inhibitory effect on HIV-1 protease and integrase activity.[51] Rutin (*Satureja*) has a strong interaction with 3CLpro and ACE2 and has significant antibacterial and antiviral power.[52,53] This molecule has demonstrated an antiviral effect against avian influenza strain H5N1.[54] An in vitro study has shown that Genkwanine (*Rosmarinus officinalis L*) has an antiviral activity. It was identified as a potent anti-ASFV compound that targets viral entry and replication.[55] Thus, the present study revealed that Genkwanine is able to bind with the catalytic dyad, and is thereby anticipated to interrupt the 3CLpro activity. Luteolin-glucoside (*Satureja*) activity was demonstrated as a neuraminidase inhibitor against influenza A virus infection in cell culture and mice.[56] Ultimately, based on the available evidence, these natural compounds can have 2 effects at once, inhibiting 3CLpro and preventing recognition between the virus and ACE2.

Conclusion

Molecular docking analysis revealed that Taxol, Rutin, Genkwanine, and Luteolin-glucoside exhibit strong interactions, in terms of binding energy, with the targets of SARS-CoV2 and human ACE2. The results of our study are consistent with other experimental studies that have demonstrated antiviral potency. Therefore, we suggest that these naturally occurring molecules could be effective against COVID-19.

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Author Contributions

All authors contributed to the conception and design of the study, and drafting of the manuscript.

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