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Oleanolic Acid, Ursolic Acid and Apigenin from *Ocimum basilicum* as Potential Inhibitors of the SARS-CoV-2 Main Protease: A Molecular Docking Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The present study aims at identifying potential inhibitors from a set of ten compounds from *Ocimum basilicum* against the SARS-CoV-2 main protease, the chymotrypsin-like protease (3CLpro).
Materials and Methods: Computational studies by molecular docking (Autodock tool) were used to obtain the scoring function of ten phytochemicals in interaction with the SARS-CoV-2 main protease. The pharmacokinetic behavior of the high-docking score compounds was addressed by using SwissADME and pkCSM webservers.
Results: Three high-docking score ligands were identified as hit compounds mainly the oleanolic acid (-8.55 kcal/mol), the ursolic acid (-8.21 kcal/mol) and apigenin (-7.52 kcal/mol). Their pharmacokinetic profile revealed that they have good therapeutic profile of druggability and safe. The biological activities of the three compounds especially their anti-inflammatory properties in relation with the excessive production of proinflammatory cytokines in the most severe form of the COVID-19 were also highlighted.
Conclusion: COVID-19 outbreak is a serious public health threat that requires immediate action. In order to combat this pandemic, several strategies are used and the identification of potential inhibitors of the main protease of the virus is one of the widely used strategies. Here, three potential inhibitors from *Ocimum basilicum* plant (leaves) were pinpointed. Further *in-vitro* and *in-vivo* studies are needed that will clarify the role of *Ocimum basilicum* for the management of COVID-19 disease.

Keywords: Ocimum basilicum; COVID-19; hit compound; pharmacokinetic profile; SARS-CoV-2 main protease.

1. INTRODUCTION

Over the last two decades, two prior outbreaks have emerged in the world as epidemics; Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) which was first reported in November 2002 in Guangdong, China, and Middle Eastern Respiratory Syndrome (MERS-CoV) which was first reported in Saudi Arabia in 2012 [1]. In December 2019, an outbreak of unidentified pneumonia cases which was first reported in December 2019 in Wuhan, China, has become the third and the most recent coronavirus outbreak, called Coronavirus disease (COVID-19) [1]. This CoV outbreak is caused by the SARS-CoV-2. Data from www.worldometers.info/coronavirus states that, on January 28, 2021, COVID-19 had already infected 101,541,959 people, caused 2,186,916 mortalities and 73,452,519 recovered people around the world. The most commonly affected organ system by COVID-19 is the respiratory system, with the most frequent clinical manifestations including fever, cough, fatigue, dyspnea, and sore throat [2]. Based on the relevant clinical characteristics of the SARS-CoV-2 patients, the virus enters the cell via angiotensin-converting enzyme-2 (ACE-2), leading to severe injury in the lungs (pneumonia) and dissemination of the virus to several other organs that may be infected in the course of illness. The extra-pulmonary clinical manifest tations of COVID-19 that affect other organs like liver, cardiovascular, ocular, gastrointestinal are elevated bilirubin, heart failure, epiphora, abdominal pain, etc [2-3]. Pathophysiologically, the most important feature is that in the most severe cases, SARS-COV-2 patients develop an acute inflammatory lung injury, with hyperproduction of proinflammatory cytokines [4-5]. This abnormal production of proinflammatory cytokines can lead to both acute respiratory distress syndrome (ARDS) and acute cardiac damage, and thus to death [6]. The current epidemiological data suggests that men are more affected than women by the COVID-19 virus. Kopel *et al* reported that women are less susceptible to viral infections than men due to their mounting of more robust immune responses [7]. Oertelt-Prigione hypothesized that this effect could result from an increase in the production of cytokines, chemokines and interferons in females than males [8]. Data on the component of race in the manifestations of the COVID-19 reveals that minority groups may be more susceptible to COVID-19 infections given their low socioeconomic status that may be a contributing factor to the higher presence of comorbidities and thus to the prevalence of COVID-19 infections [9-10].

Corona viruses are enveloped, positive single-stranded RNA viruses with large genome size ranging from 26 kb to 32 kb. These viruses are

representative of four subfamilies, which include alpha-, beta-, gamma- and delta-coronaviruses. Comparative genomic studies have shown that SARS-CoV-2 belongs to the *beta-coronavirus* family and is phylogenetically very similar to SARS-CoV-1 than MERS-CoV (Middle East Respiratory Syndrome Coronavirus) [11]. Due to the similarities of 79% and 96% for complete genome sequence recognition rates of SARS-CoV and bat SARS-CoV (SARSr-COV-RaTG13), it's suggested that bats may be the hosts of CoV viruses [12]. Similarly, for SARS-CoV-2 there may exist original, intermediate and final hosts and so the disease may transfer from infected animal to human.

To date, no drug has yet been found and the COVID-19 remains a global pandemic with little treatment options. However, the first generation of COVID-19 vaccines begins to emerge and several countries already approved their use. On this basis, some FDA approved drugs such as lopinavir, ritonavir, and sofosbuvir, formerly used against SARS-CoV, MERS-CoV, HIV and Ebola virus are used for the management of patients with COVID-19 [13].

Another therapeutic option to tackle the virus is to assess the efficiency of plant secondary metabolites and other nutraceuticals against SARS-CoV-2 proteins [14]. In fact, traditional medicine appears to be a prime candidate for the treatment of COVID-19 because of its multiple proofs in the treatment of different diseases [15-16]. Medicinal plants possess several molecules with biological activities such as antiviral, antioxidant, anthelmintic, antifungal, etc. [17-18]. The World Health Organization has revealed that more than 80% of the African population uses medicinal plants to relieve their ailments due to problems related to the accessibility, cost and sometimes undesirable effects of some modern products [19-20].

One of the medicinal plants known for its multiple biological properties is *Ocimum basilicum,* belonging to the Lamiaceae family. It is an aromatic plant containing many secondary metabolites, macro and micronutrients and its essential oil contains several chemical compounds such as estragole, linalool, 1,8-cineole, etc., which confers to the plant its antiviral activity [21-22].

Earlier studies have shown that *Ocimum* species can represent potential bio resources for the management of COVID-19 owing to its well-documented antiviral activity [23]. As it is a challenging process to develop new molecules to be used for the treatment of diseases, this study is designed to screen ten phytochemicals from *Ocimum basilicum* to identify potential inhibitors of the main protease of the SARS-CoV-2 (Mpro). To do so, virtual or computational screening by molecular docking was used in order to assess the efficiency of the potential inhibitors by means of the binding affinity of ligand-protein complex. The pharmacokinetic behavior of ligands was established using pkCSM web server.

2. MATERIALS AND METHODS

2.1 Literature Review

Data published on *O. basilicum,* the chemical compounds (phytochemistry) and their antiviral activities have been collected in the online bibliographic databases, such as Google scholar, DOAJ, PubMed, PubMed Central, Science Direct, SCIELO and Science alert [21-24].

2.2 Molecular Docking

2.2.1 Protein preparation

The corona virus encodes more than one dozen proteins, among these, the chymotrypsin-like protease (3CLpro) is the most studied. Based on its function, the 3CLpro or the COVID-19 virus Main protease (Mpro) is a key CoV enzyme which plays a pivotal role in mediating viral replication and transcription, and is suggested to be a potential drug target to combat 2019-nCov, which is highly conservable among corona viruses [25].

Several proteins that play a key role in COVID-19 viral infection and are considered as potential pharmacological targets have recently been described. These include: 3CLpro (coronavirus main protein); PLpro (papain-like protease); RdRp (RNA-dependent RNA polymerase); S protein (viral spike glycoprotein); TMPRSS2 (transmembrane protease serine 2); ACE2 (angiotensin-converting enzyme 2); and AT2 (angiotensin AT2 receptor) [26]. 3CLpro/Mpro (PDB ID: 2GTB) is currently recognized as one of the most studied pharmacological targets in the research and development of anti COVID-19 drugs, particularly in terms of both number of patents and number of potential drug candidates [25]. It is a proteolytic enzyme necessary for the cleavage of viral polyprotein into several functionally active protein units. Its choice as a

pharmacological target in this study is justified by the fact that its active site is perfectly conserved and would not be affected by mutations. In addition, the high level of homology with 3CLpro/Mpro SARS-CoV-1 (~96%) allows the use of clinically approved anti-SARS-CoV-1 drugs as positive controls in the virtual screening for validation in clinical research for anti-SARS-CoV-2 drugs [12].

The crystal structure of Mpro (PDB ID: 6LU7) was retrieved from the Protein Data Bank (PDB) and imported into Discovery studio visualizer for identifying the amino acids in the binding pocket. The analyzed structure was further imported into Auto dock 4.2 [27] where the inhibitor and water molecules were removed before the docking and hydrogen atoms were added to the protein in order to correct the ionization and tautomeric states of the amino acid residues. Kollman charges were added to the protein and was saved in .pdbqt format. Fig. 1 below displays the complex between COVID-19 Mpro and the co-crystallized inhibitor 2GTB, which is the main protease found in the CoV associated with the severe acute respiratory syndrome (SARS). The co-crystallized ligand N3 (also called the native inhibitor) was used to define the binding site which were centered _x = 8.87000157133, y = -12.6801094604 and z = 14.2751403901 with the size x = 25.1171537474, y = 31.5301060003 and z = 32.0783937479)

2.2.2 Generation of ligand data set

The selected compounds (1-10, see name at Table 1) used as ligands [21-24] and drawn using ACD/Marvin Sketch (20.9) [28]. Fig. 2 shows their 2D structures. Furthermore, the ligands were imported into Chem Draw to obtain 3D from 2D. The 3D ligands were saved in .pdf format. The ligands were then imported into Auto dock 4.2 interface tool and saved to pdbqt format.

2.2.3 Docking strategy

Autodock tool was used to generate the bioactive binding poses of ligands dataset in the active site of COVID-19 Mpro. The protein coordinates from the bound ligand of 6LU7 was used to define the binding active site. Further, scoring function was calculated using the standard protocol of Lamarckian genetic algorithm. The grid map for docking calculations was centered on the target protein. Accelrys Discovery Studio 2019 software was used to model non-bonded polar and hydrophobic contacts in the inhibitor site of 6LU7. The docking result was visualized using Pymol 2.3.4.0 and Discovery Studio Visualizer 4.0.

The docking strategy used to find potential inhibitors from *O. basilicum* against the SARS-CoV-2 Mpro can be pictured as follows (Fig. 3).

3. RESULTS

3.1 Molecular Docking Study

Auto dock 4.2 was used to assess the binding affinities and analysis of main interactions between the COVID-19 Mpro and *O. basilicum* compounds was performed in Pymol 2.3.4.0. Several compounds from *O. basilicum* have been reported to show antiviral bioactivities. We investigated ten compounds from this plant as potential inhibitors of the COVID-19 Mpro. Docking poses were primarily ranked by the binding affinity of their best scoring conformation. The free enthalpies (binding affinity) obtained from docking of 6LU7 with ten compounds from *O. basilicum* are given in Table 1. Also gathered in this table are the IUPAC name and the PubChem ID of each compound.

The Auto dock binding energy values range from -4.79 to -8.55 kcal/mol and reveal three best docked compounds with highest binding affinities: oleanolic acid/ligand 1 (-8.55 kcal/mol), ursolic acid/ligand 10 (-8.21 kcal/mol) and apigenin/ligand 2 (-7.72 kcal/mol). These three compounds have binding energy higher than that of the ligand reference with the binding energy computed to -7.40 kcal/mol. Inspection of table 1 also reveals a strong competition between complexes formed by ligands 3,4,5, 6,7,8, and 9 with the Mpro. One can easily see that all the complexes formed between these different compounds and the virus protease have about 5 kcal/mol of the binding energy. Consequently, only molecules 1, 2 and 10 should have better antagonistic properties than the others compounds.

As depicted in Fig. 4, the greatest contribution to the stabilization of the complexes comes from hydrogen bonding interaction that involves O-H and C=O groups of the ligands that can act simultaneously as donor and acceptor [29]. Nevertheless, other significant contributions to the stability of the complexes come from π-π (Stacking and T-shaped) and π-alkyl interactions that are controlled by dispersions forces [30-31].

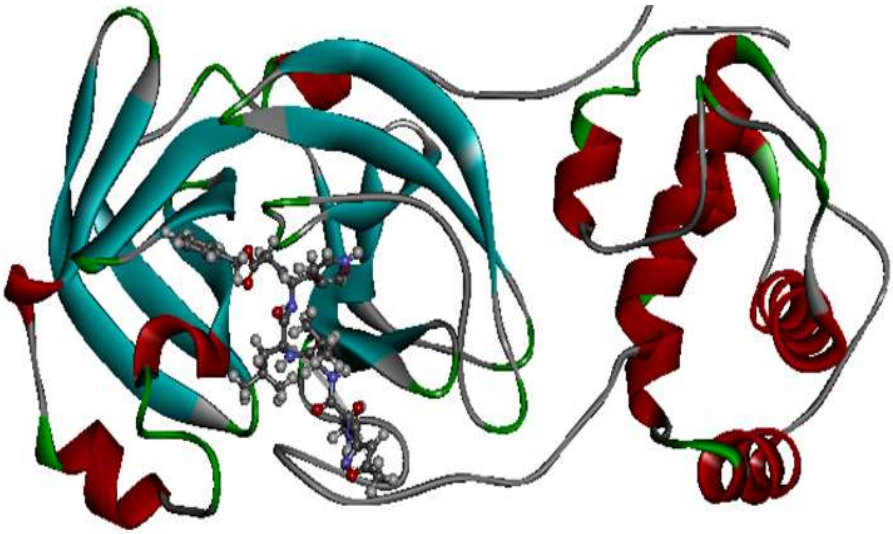

Fig. 1. Complex between COVID-19 Mpro and the co-crystallized inhibitor 6LU7

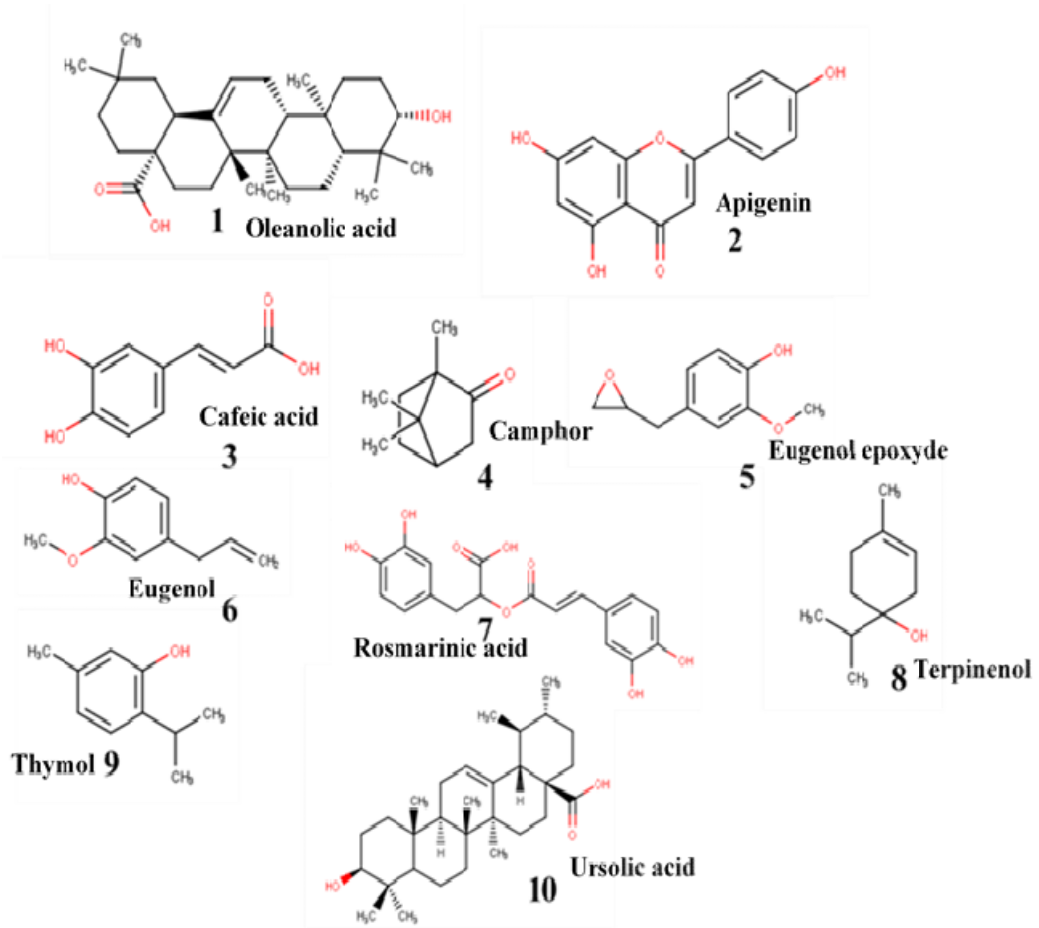

Fig. 2. Structures of compounds 1–10 derived from *O. basilicum*

H-bond distances and angles between the protein target and the 1,2 and 10 ligands along with the involved groups of ligands in the H-bonds as well as the interacting residues of the three best docked ligands from *O. basilicum* are gathered in Table 2.

The interactions analysis of three best-docked ligands with Mpro can be summarized as follows:

The 2D diagram from Fig. 4 shows that ligand 1 formed four hydrogen bonds with the residues THR26, GLU166, HIS164 and CYS145. These H-bonds are supported by? van der Waals (vdW) interactions with the residues ARG188, ASP187, GLY143, THR25, ASN142, and GLN189. Finally, the presence of five rings in the compound offered the possibility of alkyl and π-alkyl with the residues MET165, HIS41 and MET49.

In the complex with ligand 2 and the Mpro, two hydrogen bonds were formed with the residues ASP187 and THR190; seven vdW with the residues TYR54, ARG188, GLU166, LEU167, ALA191, GLN192 and GLN189. Two of the three aromatic rings of the ligand 2 participate in interactions, π-π T-shaped interaction with HIS41 and π-alkyl with MET165. Another interesting interaction arises from the S atom of this latter amino acid (MET165) with the O atom located in the second aromatic ring. This is a chalcogen bond that derives from an attractive interaction involving a chalcogen atom (O, S, Se) as the Lewis acid and a Lewis base. Chalcogen bonds are relatively strong and highly directional [32].

Finally, ligand 1, which has a similar structure with ligand 10, formed two hydrogen bonds with the residues GLU166, GLN189 and THR24; eight vdW interactions with the residues HIS164, LEU141, MET165, SER144, ASN142, GLY143, THR26 and THR25, and alkyl/π-alkyl interactions with the residues CYS145, HIS163, and MET49.

Fig. 5. shows the three best docked ligands in the binding pocket of the SARS-CoV-2 main protease.

3.2 Drug-Likeness and ADMET Prediction

Computational chemistry methods and bioinformatics tools are widely used in the field of drug design and for understanding the electronic properties of various drug-molecules [33-40]. After identifying hit compounds, the next step to deal with in the pipeline of computer-aided drug design is the pre-clinical optimization that concerns the physicochemical properties, the prediction of absorption, distribution, metabolism and excretion (ADME), as well as the *in silico* evaluation of toxicity.

Pharmacokinetic profiles of the three top hit molecules were evaluated according to Lipinski's rule-of-five that fixes criteria for a compound to exhibit drug likeness: molecular weight < 500 Daltons (Da), calculated lipophilicity (Log P) < 5, number of hydrogen-bond acceptors < 10, and number of hydrogen bond donors < 5 [41]. In silico physicochemical parameters of the hit compounds are summarized in Table 3.

Inspection of Table 3 shows that all hit compounds exhibit good bioavailability and drug-likeness by fulfilling Lipinski's criteria. In addition, the three high dock-scoring ligands have good solubility (an S log value lower than -4.00) which reflect good absorption and better elimination by the urinary tract [42]. Further, according to Cerqueira and co-workers, for optimal drug absorption and distribution, the polar surface area (PSA) values cannot be higher than 140 Å [43]. The PSA values of the hit compounds that range from 57.53 to 90.90 Å are an indication of a good therapeutic profile of druggability.

Another view of pharmacokinetic profile analysis for the three best docked compounds was performed using the pkCSM webserver. The corresponding results are listed in Table 4.

The human intestine absorption (HIA) values reveal that hit 1 has the highest probability of being absorbed by human intestine (99.931%), followed by hit 2 (93.250%) and then hit 3 (81.132%). The recommended value of the skin permeability for a drug-molecule, which is an important consideration for improving drug efficacy, is set at more than -2.5 cm/h [44]. Surprisingly, all the three hits have exactly the same value of skin permeability (-2.735) and can be predicted to have good skin penetrability. The volume of distribution (VD) is a parameter related to the distribution of a drug to tissue. The higher the VD is, the larger the amount of a drug is distributed to tissue rather than plasma [44]. Therefore, from Table 4, it can be seen that hit 2 have good distribution than hits 1 and 3. Molecules are able to pass through the blood brain barrier promptly when log BB is higher than 0.3. Consequently, since log BB values of the three hits compounds are not higher than 0.3, they are able to penetrate the blood-brain barrier moderately.

With regards to the two main isoforms responsible for drug metabolism which are P2D6 cytochrome (CYP2D6) and P3A4 cytochrome (CYP3A4) [5,44], the three hit compounds do not affect or inhibit these two enzymes.

Turning next to excretion also called elimination, the total clearance is directly linked to the renal OCT2 (organic cation transporter 2) substrate that offers helpful information on potential contraindications of a drug-molecule. The three high-docking score compounds are predicted to be not renal OCT2 substrates. This means that they can be eliminated through the OCT2 substrate.

Finally, the toxicities prediction reveal that the three ligands did not confer mutagenic, and they are non-hepatotoxic, except hit 1 which is predicted to be hepatotoxic. Their oral acute toxicity (LD_{50}) are classified in category or class 4, meaning that they are slightly toxic (Globally Harmonized System: 300 < Category 4 ≤ 2000) and can thus be considered as safe.

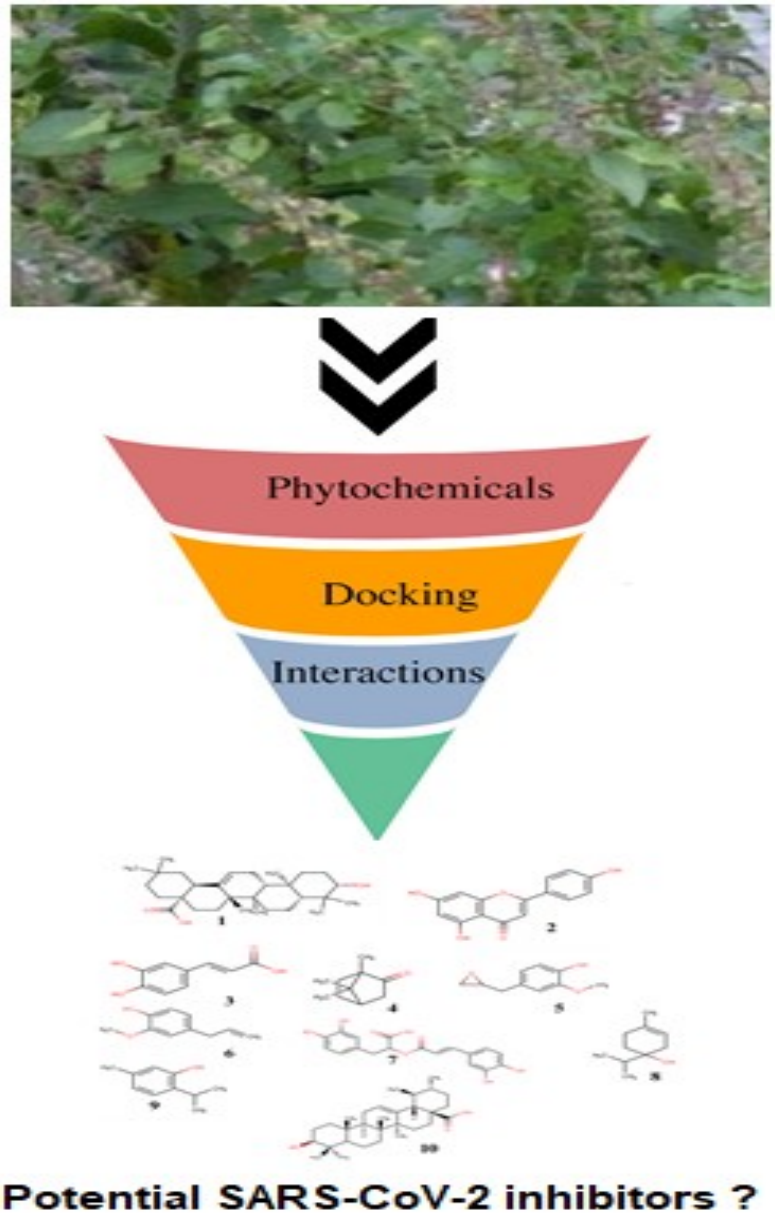

Fig. 3. Docking strategy to identify potential inhibitors from *O. basilicum* against Mpro

Table 1. Free enthalpies of binding (kcal/mol) from molecular docking calculations

N°	Compound name	IUPAC name	Pub Chem ID	Binding affinity
1.	Oleanolic acid	(4aS,6aR,6aS,6bR,8aR,10S,12aR,14bS)hydroxyl-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid.	10494	-8.55
10.	Ursolic acid	(1S,2R,4aS,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid.	64945	-8.21
2.	Apigenin	5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1 benzopyran-4-one	5280443	-7.72
	Ref_Ligand			-7.40
4.	Camphor	1,7,7-triméthylbicyclo[2,2,1] heptan-2-one	2537	-5.64
8.	Terpinenol	4-méthyl-1-(propan-2-yl) cyclohex-3-én-1-ol	11230	-5.43
7.	Rosmarinic acid	(2R)-3-(3,4-dihydroxyphenyl)-2-{[(2E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy} propanoic acid	5315615	-5.24
9.	Thymol	2-Isopropyl-5-methylphenol	6989	-5.19
5.	Eugenol epoxyde	Epoxy-4-Allyl-2-methoxyphenol	12304196	-5.12
6.	Eugenol	4-Allyl-2-methoxyphenol	3314	-5.02
3.	Cafeic acid	3,4-Dihydroxycinnamic acid	689043	-4.79

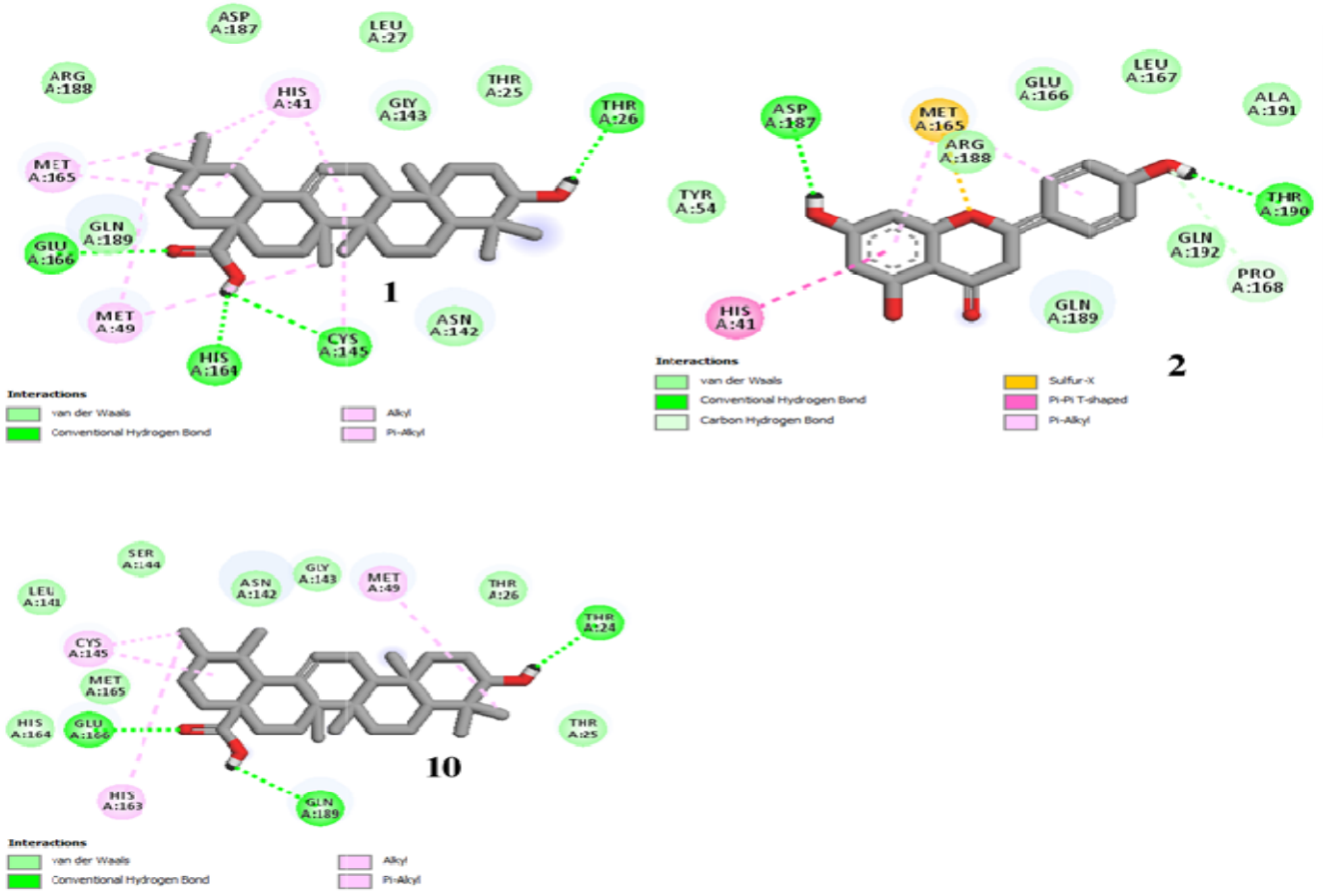

Fig. 4. 2D interactions map for ligands 1, 2 and 10 with COVID-19 Mpro

Table 2. Hydrogen-bonds parameters (distances and angles) derived from docking of COVID-19 Mpro with the three best docked ligands

Ligand	AA residues	Ligand group	δ (Å)	θ(˚)
1	GLU166	O=C_2	1.39	150
	HIS164	H-O	1.34	133
	THR26	H-O	2.01	164
	CYS145	H-O	2.12	159
2	ASP187	H-O	2.01	153
	THR190	H-O	1.87	175
10	GLU166	O=C_2	1.99	185
	GLN189	H-O	2.01	165
	THR24	H-O	2.00	135

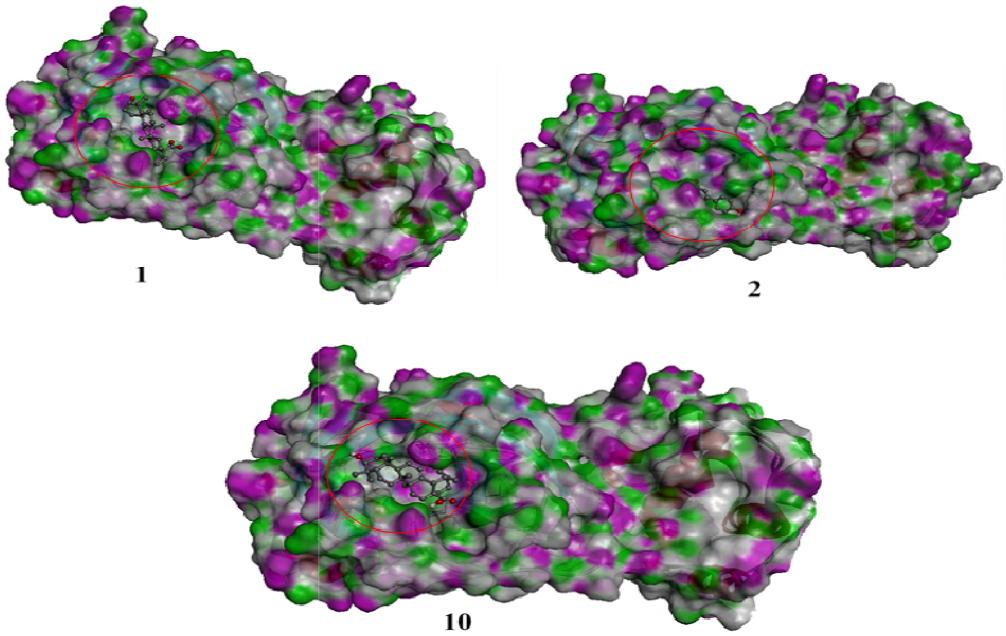

Fig. 5. Three best docked ligands in the binding pocket of COVID-19 Mpro of 6LU7 (1, 2 and 10)

4. DISCUSSION

Since early civilization, humans have used medicinal plants in different systems of traditional medicine to treat various ailments [45]. Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. The COVID-19 outbreak is characterized by rapid transmissibility and the lack of specific drugs. Thus, the search for effective therapeutic molecules is being intensified and virtual screening can save time.

Proteins such as 3CLpro (coronavirus main protease), PLpro (papain-like protease), RdRp (RNA-dependent RNA polymerase), S protein (Viral spike glycoprotein), TMPRSS2 (Transmembrane protease serine 2), ACE 2 (Angiotensin converting enzyme 2), AT2 (Angiotensin AT2 receptor) play a key role in COVID-19 viral infection and are considered as potential pharmacological targets [26]. In drug discovery, the best anti COVID-19 drug candidate is the molecule that can specifically bind to one of the above-mentioned pharmacological targets to form a stable complex. The docking of ten natural compounds derived from *Ocimum basilicum* led us to the identification of three high dock-scoring compounds: oleanolic acid (ligand 1), ursolic acid (ligand 10) and apigenin (ligand 2). It is worthy to highlight that these three compounds have already each shown biological activity.

Table 3. In silico physicochemical parameters using Swiss ADME online tool

Ligand	Formula	MW (<500 Da)	Log P* (<5)	HBD (<5)	HBA (<10)	PSA (Å)	Violations	Log S
1	$C_{30}H_{48}O_3$	456.70	3.93	2	3	57.53	0	-3.07
2	$C_{15}H_{10}O_5$	270.24	1.89	3	5	90.90	0	-3.32
3	$C_{30}H_{48}O_3$	456.70	4.01	4	6	57.53	0	-3.07

*With MW= Molecular weight, Log P = Lipophilicity, PSA = Polar Surface Area, Log S = water solubility. *Log P stands for Partition Coefficient i.e. the ratio between the partition coefficients of 1 Octanol and water. cLogP breaks down the compound into small fragments and then calculates the Log P.*

Table 4. Pharmacokinetic profile of the three high dock-scoring compounds.

Parameter	Ligand 1	Ligand 2	Ligand 10
Absorption & Distribution			
HIA (%)	99.931	93.250	81.132
Skin permeability (log K_p)	-2.735	-2.735	-2.735
VDss (human) (log L/kg)	-1.085	0.822	-1.088
BBB permeability (log BB)	-0.140	-0.734	-0.141
Metabolism			
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Excretion			
Total clearance	-0.081	0.566	0.083
Renal OCT2 substrate	No	No	No
Toxicity			
Mutagenicity (Ames test)	No	No	No
Hepatotoxicity	Yes	No	No
Skin sensitisation	No	No	No
Oral rat acute toxicity (LD_{50}, in mol/kg)	2.349 1175	2.450 1225	2.346 1173

The oleanolic acid, a triterpenoid known for its antibacterial activity [46], also exhibit anti-inflammatory effect [47]. The ursolic acid, a pentacyclic triterpenoid carboxylic acid which is the major component of many plants including apples, basil, cranberries, peppermint, rosemary, and prunes has been reported to possess antioxidant, anti-tumor, anti-inflammatory [48] and also anti-sickling properties [49]. It should be noted that ursolic and oleanolic acids, both triterpenic acids are isomers. Indeed, a survey of literature reveals some benefits and risks about the use of acids for the management of COVID-19. Ramachandran *et al* reported that patients with COVID-19 may use antacids and acid-reducing medications [50], while Bianconi *et al* revealed that since acetylsalicylic acid has anti-inflammatory and antithrombotic effects, as well as some antiviral activity against DNA and RNA viruses, it might be a potential therapeutic candidate that has to deserve further attention [51].

The apigenin, which is a flavonoid compound, exhibits antibacterial [52] and also anti-inflammatory activity [53]. In fact, it is important for a compound that represents a potential inhibitor of the SARS-CoV-2 main protease to have an anti-inflammatory property, since in the most severe cases of the disease; there is an excessive production of proinflammatory cytokines [4-5]. This compound was also identified as a potential candidate for inhibiting the viral replication and for controlling inflammation during COVID-19.

Recently, the anthelmintic niclosamide has received attention as a potential therapeutic agent tackling the virus through different mechanisms [54]. Interestingly, Ocimum species which could potentially offer antiviral effects [23], one of its genus mainly *Ocimum basilicum* have been reported to show the anthelminthic activity [55]. To this effect, it is not excluded that a phyto-drug based on *Ocimum basilicum* extracts can attenuate in the patient the expression of pro-inflammatory factors and receptors likely to induce acute respiratory distress which is the main cause of mortality associated with COVID-19 while strengthening the immune system.

Another interesting facet is to compare the binding energies of the three best docked compounds with those of FDA approved drugs repurposed for COVID-19. Previous study reported the binding sites residues of Lopinavir and Nelfinavir with Mpro and the docking scores were assessed to −8.4 and -8.1 kcal/mol, respectively [12]. Compared with Lopinavir and Nelfinavir which are protease inhibitors recommended for the treatment of SARS and MERS, the docking affinity scores of the three hit compounds are very close to those of two anti-HIV drugs, even a bit higher for hits 1 and 10.

The results provided here can be associated with other previous studies highlighting the antiviral activities of some safe herbal plants which could be used in the management of COVID-19 [56-57], and accordingly, constitute a panoply of plants which, when they are consumed, one can

strength the immune system and prevent the disease. But is must be underscored that this study is solely on *in-silico* investigations, so, *in-vitro* and *in-vivo* studies are needed that will clarify the role of the 3 compounds for the management of COVID-19 disease.

5. CONCLUSION

COVID-19 pandemic is a major public health threat that requires immediate action. Due to the urgency of the situation, plants biodiversity provides a plethora of compounds that may offer treatment options. We reported in this study the evaluation of the efficiency of ten compounds derived from *Ocimum basilicum* against the SARS-CoV-2 (COVID-19) main protease through molecular docking. The scoring function led us to pinpoint three potential inhibitors of the enzyme, mainly the oleanolic acid (ligand 1/-8.55 kcal/mol); the ursolic acid (ligand 10/-8.21 kcal/mol) and apigenin (ligand 2/-7.72 kcal/mol). The pharmacokinetic behavior of the three high dock-scoring compounds from ADME analysis showed a good predicted therapeutic profile of druggability. Finally, their toxicities prediction reveal that they are safe and thus, they can serve as potential anti-SARS-CoV-2 lead molecules for further optimization and drug development processes to combat COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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