MINOR COMPOSITION COMPOUNDS OF ALGERIAN HERBAL MEDICINES AS INHIBITORS OF SARS-CoV-2 MAIN PROTEASE: MOLECULAR DOCKING AND ADMET PROPERTIES PREDICTION

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ABSTRACT

The identification of drugs against the new coronavirus (SARS-CoV-2) is an important requirement. Natural products are substances that serve as sources of beneficial chemical molecules for the development of effective therapies. In this study, 187 natural compounds from Algerian herbal medicines were docked in the active site of SARS-CoV-2 main protease. The result indicates that Piperitol, Warfarin, cis-calamenen-10-ol and α-Cadinene are the structures with best affinity in the binding site of the studied enzyme and all of them respect the conditions mentioned in Lipinski's rule and have acceptable ADMET proprieties; so, these compounds could have more potent antiviral treatment of COVID-19 than the studied compounds, and they have important pharmacokinetic properties and bioavailability.

Keywords: COVID-19, SARS-CoV-2, Algerian herbal, Natural compounds, Piperitol, ADMET, Molecular Docking.

1. INTRODUCTION

Emerging or re-emerging epidemic diseases pose a continuing threat to global health security, including Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV) [1], Middle East Respiratory Syndrome (MERS-CoV) [2], and recently a contagious respiratory illnesses called COronaVirus Infectious Disease 2019 (COVID-19) [3]. This later, highly publicized, is the most dangerous, which declared pandemic by WHO in March 2020 [4]. It is caused by infection with a new coronavirus, known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified firstly in December 2019 in Wuhan (China) [5]. This novel beta-coronavirus is a positive-sense single stranded RNA virus with a genome of about 30 kb with structured untranslated region; belonging to the family coronaviruses and subgenus sarbecovirus (beta-CoV lineage B), but it differs from previously known SARS-CoV and MERS-CoV [6]. It bears about 80% genome homology with SARS-CoV and has about 96% identical genes with the bat coronavirus [3]. Symptom of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death [7] which fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat are common symptoms seen in adults [8]. Among others, and according to Siordia Jr. The most common comorbidity is hypertension (30.7 %), followed by diabetes mellitus (14.3 %) and cardiovascular diseases (11.9 %) [9].

So far, all researchers agree that there is no specific treatment for COVID-19. So, without any effective antiviral agents and no approved human coronavirus vaccines available at present, and to prevent respiratory aerosol/droplet infection generated by individuals who are symptomatic, and further spread of COVID-19, some precautions are recommend for avoiding COVID-19, as isolation of the patient, hand hygiene measures, use of face masks and other sanitary measures. This will reduce the risk of transmission to care givers and close contacts [3,10]. Current treatments focus on managing symptoms along the course of infection [11]. Meanwhile, numerous research laboratories are currently seeking a treatment that can eliminate the MERS-CoV infection, by searching for new more specific alternatives for the virus [12]. A need for effective vaccine is being seen an as good preventive strategy in this pandemic [3]. So, a variety of antiviral agents and symptomatic treatments are being administered to patients and urgent clinical trials are underway, thus under these circumstances, it is important to explore various possibilities for the treatment of COVID-19 including herbal medicines [13]. Clarification transmission routes and pathogenic mechanisms, and identification of potential drug treatment targets will promote the development of effective prevention and treatment measures [14].

Basis on its historical experience and holistic pharmacological action, traditional Chinese medicine (TCM) could be used as an alternative treatment option or in combination with Western medicine to treat COVID-19 [15]. TCM was used in 91.50% of the COVID-19 cases in China, showing encouraging results in improving symptom management and reducing the deterioration, mortality, and recurrence rates [16]. Many medicinal herbs were used in TCM formulae for treating COVID-19 in China [17,18], some of them has been prescribed to COVID-19 patients according to the status of their disease (mild, moderate, severe, and critical stages) [11, 17]. Panyod et al. summarize the antiviral activity of foods and herbs against influenza virus [19], and results of ongoing clinical trials on hydroxychloroquine, azithromycin alone or in combination and a new antiviral agent remdesivir may help to treat some of the infections [3]. Unfortunately, the two first drugs have toxic effects and their use in high doses can create major risks for patients [20,21].

Based on in vitro and in vivo studies, promising compounds in traditional medicine can be used as effective antiviral drugs for the treatment of diseases caused by SARS-CoV-2 [14]. The anti-CoVs effects of natural compounds and their possible action mechanisms are reported in the literature review of Xian et al. [22]. These molecules can act as inhibitors of replication, membrane fusion and assembly of SARS-CoV-2 [23]. Additionally, computer molecular docking shows that these monomers have good binding ability to COVID-19 virus and host targets [14]. Despite, promising results obtained from molecular docking of selected drugs with potential targets do not guarantee the effectiveness of a drug in treatment under clinical conditions; however, these works provide a general idea of where research should go [24].

In this paper, 187 natural compounds were docked into the active site of SARS-CoV-2 main protease to predict the mode of binding between these molecules and their potential target (SARS-CoV-2 main protease), also to determine the affinity of these molecules in the binding site of the studied enzyme. The study is followed by a prediction of Lipinski's rule and ADMET parameters of the studied compounds, chloroquine and hydroxychloroquine; the aim of which is to find substances more effective than chloroquine and hydroxychloroquine which do not have toxic effects of these two drugs.

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2. MATERIALS AND METHODS

2.1. Data Collection

This article constitutes the continuation of our previous work about major components of medicinal plants collected from Algerian pharmacopeia which were docked in the active site of SARS-CoV-2 main protease as possible inhibitors. unlike major compounds, the minor's ones are generally neglected in scientific research. These compounds may elicit some activity, while in pure form, against organisms although the proportions of such compounds in the plant were considerably low; on the other hand, minor components are critical to the activity and may have a synergistic effect or potentiating influence.

Species chosen are those found in bibliographic data and which are used in Algerian traditional medicine in the treatment of diseases of the respiratory system including cough, Rhinitis, Bronchitis, Asthma, Influenza, Flu and Pulmonary diseases in general, according traditional Algerian pharmacopeia

In this work, we have selected 187 compounds extracted from 24 different aromatic and medicinal plants from Algeria; Table 1 shows information on the plant of origin of each compound used as well as their percentages in the plant. The selection is based on these criteria:

• Traditional medicinal use: based on infections and diseases related to the respiratory system;

• The chemical constituents are those declared minority by the authors;

• All items declared correspond to medicinal species collected in Algeria.

Table 1. Chemical composition of medicinal plants and their percentages.

N°	Minor constituents (%)	Scientific/ (Common) Name	Therapeutic use*					Used parts	Ref.
			1	2	3	4	5		
1	α-Thujone (0.6), Aldehydeperrilique (0.6), β-Caryophyllene (0.6), Alcool perrilique (0.5), 3,4-Dimethyl cinnoline (0.4),nor β-Calamenene (0.4), α-Copaene (0.1)	*Artemisia arborescens L.* (Sayba, siba, sejert meriem)	✓					Aerial part, leaves	[25]
2	Limonene (0.3), 6,8-Nonadien-2-one,6-methyl-5-(1-methyletildene) (0.3), γ -Muurolene (0.3), α-Zingiberene(0.3), Methyl p-tert-buthylphenil acetate (0.3), 3-Otadecine (0.3)	*Peganum harmala* L. (Harmel)	✓					Aerial part, seeds	[26]
3	(E)-Salvene (0.1), cis-Verbenol (0.1), Borneol (0.1), Thymol (0.1), Z-β-Damascenone(0.1), Aromadendrene (0.1), δ-Cadinene (0.1), Spathulenol(0.1), Caryophyllene oxide (0.1)	*Pinus halepensis* Mill. (Sanouber halabi)	✓		✓	✓		Resin, fruits, leaves and tree bark	[27]
4	(z)-Tetradec-9-enoic acid (0.3), (E)-Tetradec-9-enoic acid (0.3), Methylhexadecanoate (0.2),Ethylheptadecanoate (0.3), Ethyloctradecanoate (0.3%), Tricosane (0.3), Tetracosane (0.3), Hexacos-9-ene (0.2), Hexacosane (0.3)	*Ziziphus lotus* L. (Sedra)	✓					Leaves, Roots	[28]
5	Benzene (0.3), Cyclohexane (0.3), 2, 3- Butanediol(0.4), *cis*-2-Hexenal(0.3), 3-Hexen-1-ol (0.3), 1-Hexanol (0.5%), Nonanal (0.5)	*Marrubium deserti* de Noé (Temiriouet er'rmel)	✓	✓	✓	✓	✓	Whole plant	[29]
6	Camphene (0.1), β-Pinene (0.2-0.4),Myrcene (0.1-0.4), y-Terpinene (0.2-0.3), Carvenone (0.2), Pinocarvone(O.1-0.3), Aromadendrene (0,2-0,6), Terpinen-4-01 (0,3-0,5), Allo-aromadendrene (0.1-0.5), α-Terpineol (0.1), δ-Terpineo (0.1), p-Mentha-l(7),8-dien-2-ol (0.2-0.3), p-Cymen-8-01 (0.4), trans-Carveol (0.1), Piperitol (0.2), epi-Globulol (0.2-0.4), Globulol (0.2-0.6), α-Eudesmol (0.1-0.2)	Eucalyptus sp. (Kalitousse)	✓					Leaves	[30]
7	Sabinene (0.2-0.7)2-Phenylethyl alcohol (0.2), Indole (0.3), α-Copaene(0.2), β-Bourbonene (0.1), β-Elemene (0.2), α-Humulene (0.4), *rans*-β-Farnesene (0.3), β-Ionone (0.1), Germacrene D (0.3), Pentadecane (0.5), α-Cadinene (0.3)	*Marrubium vulgare* L. (Temiriouet)					✓	Aerial part	[31]
8	α-Thujene(0.1), Camphene(0.1), Linalool (0.1%), Borneol(0.1), α-Cubebene(0.1),α-Gurjunene (0.1), trans-Caryophyllene (0.1), β-Gurjunene (0.1), δ-Cadinene (0.1), Cadina-1,4-diene (0.1), trans-Nerolidol (0.1), Abietatriene(0.1)	*Juniperus oxycedrus* L. (Arar, Taga)	✓		✓			Aerial part	[32]
9	Limonene(0.6), Sabinène (0.4), -amorphène (0.4), Tridécanal (0.5), β-eudesmol (0,5), α-eudesmol (0,4)	*Pistacia atlantica Desf.* (Botom)	✓		✓			Resin & fruit	[33]
10	Hexanal(0.09), Octan-3-ol (0.05), 6-Methyl-hepta-3,5-dien-2-one(0.09), Terpinene-4-ol (0.07), Elemol (0.08), Megastigmatrienone2 (0.09), Ethyldibenzenothiophene (0.09)	*Genista saharae* (Tellegit)	✓	✓	✓	✓	✓	Arial parts	[34]
11	Hexane(0.2), 4-Heptanal(0.2), *trans*-Linalooloxide(0.1), Nonanal (0.2), Dihydropseudoionone(0.1), *E*-Nerolidolepoxyacetate(0.2), Ethyllinoleate (0.2), *n*-Tricosane (0.1), Tetracosane (0.1)	*Matricaria pubescens* (Guertoufa)	✓			✓		Arial parts	[35]
12	Camphene (0.20), β-Pinene (0.37), 3-Carene (0.36), Myrcene (0.11), Methyl perillate (0.92), Perilla alcohol (0.67), Spathulenol (0.35)	*Ammodaucus leucotrichus* (El-Kammoun essofi, el massoufa)	✓					Fruits, seed, leaves	[36]
13	-Terpinene(0.22), Bornyl acetate(0.50), 6 β-Guaiene(0.20), Trans-calamenene(0.12), Spathlenol(0.10), Globulol(0.19), Farnesol(0.30)	*Ephedra alata* (Alanda)	✓		✓	✓	✓	Arial parts	[37]
14	3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl) (1.32), 4-Pyridinamine(1.43), Aspartic acid(1.44), Phenol, 4-(2-aminopropyl)-(1.3), Phenol, 2-methoxy-4-(1-propenyl)-, (E)-(1.3), Retinol (1.4), Warfarin(1.43)	*Glycyrrhiza glabra* (Erg essous)	✓					Roots	[38]
15	α-Thujene (0.10-1.12), Sabinene (0.10), β-Myrcene (0.18-0.22), α-Terpinene (0.15-0.16), Methylcitronellate (0.11-0.68), Exo-2-hydroxycineole acetate (0.17-0.21), (E)-Methyl isoeugenol (0.11-0.17), γ-Elemene (0.10), Spathulenol (0.10-0.12), Cubenol (0.18), β-Eudesmol (0,15 – 024%)	*Myrtus communis* (Al-Rihan or el-halmouche)	✓	✓	✓	✓	✓	Leaves, buds, fruits	[39]
16	α-Thujene (0.15), Thuja-2,4(10)-diene (0.10), α-Terpinene (0.15), Terpinolene (0.07), Nopinone (0.10), Sabina ketone (0.14), Carvacrol acetate (0.6), α-elemene (0.03), β-Copaene (0.12), α-Guaiene (0.15), trans-β-Elemenone (0.15)	*Thymus ciliatus (Desf.)* (Zaatar)	✓		✓			Arial parts	[40]
17	α-Thujene (0.05), *α*-Phellandrene (0.01), *δ*-Carene (0.01), (*Z*)-*β*-Ocimene (0.03), *allo*-Ocimène (0.02), Thymol (0.03), Carvacrol (0.02), *allo*-Aromadendrene (0.07), *δ*-Cadinene (0.08), (*Z*)-Nerolidol (0.04)	*Thymus algeriensis* (Zaatar)	✓	✓	✓	✓	✓	Summits, young flowering twigs	[41]
18	Sabinene (0.04), *β*-Pinene (0.19), *α*-Phellandrene (0.19), *δ*-Carene (0.07), Limonene (0.17), Terpinolene (0.16), *α*-Thujone (0.07), Camphor (0.03), Naphtalene (0.08), Aromadendrene (0.10), *allo*-Aromadendrene(0.05), Germacrene D (0.03)	*Thymus vulgaris* (Zaatar)			✓		✓	Arial parts	
19	α-Thujene(0.05), *α*-Pinene (0.06), Camphene (0.02), Sabinene (0.09), *α*-Phellandrene (0.01), *δ*-Carene (0.04), *allo*-Ocimène (0.05), Isopulegol (0.10), Naphtalene (0.11)	*Mentha pulegium* (Fleyou)	✓		✓			flowering aerial parts	
20	Octane -3-one (0.03), Borneol(0.02), Thymoquinone(0.04), Eugenol (0.04), Trans-carvyl acetate (0.02), Ylangene (0.03), Cis-jasmone (0.04), α-muurolene (0.04), Cadina1-4-diene (0.03), α-cadinene (0.05), Viridiflorol (0.01), Ledol (0.01), β-eudesmol (0,01)	*Thymus numidicus Poiret* (Zaatar)	✓	✓	✓	✓	✓	Arial parts	[42]

21	p-Cymene (0.23), γ-Terpinene (0.21), 1-Octen-3 ylacetate (0.24), 3-Octanyl acetate (0.26), Carvone (0.16), Lavandulylacetate (0.23), Myrtenylacetate (0.1), B-Elemene (0.26), α-Gurjunene (0.1), Germacrene D (0.2), δ-Cadinene (0.26), α-Eudesmol (0,20)	*Ocimum basilicum* (Hbek)	✓					Aerial parts, leaves	[43]
22	Neo Allo-Ocimene (0.2), α-Terpineol (0.1), n Octyl acetate (0.2), α-Bergamotene (0.1), Bicyclogermacrene (0.2), Germacrene D (0.2), α-Amorphene (0.2), Spathulenol (0.2), γ-Eudesmol (0,2), β-Eudesmol (0,1), α-Eudesmol (0,1)	*Ocimum gratissimum* (Hbek)	✓					Aerial parts, leaves	[44]
23	1-octen-3-ol (0.1), α-terpinene (0.1), (*Z*)-β-ocimene (0.1), benzene acetaldehyde (0.1), 1-nonen-3-ol (0.1), *p*-mentha-2,4(8)-diene (0.1), myrtenol (0.1), *trans*-dihydrocarvone (0.1), verbenone (0.1), carvacrol, methyl ether (0.1), indole (0.1), β-cubebene (0.1), β-elemene (0.1), β-copaene (0.1), γ-himachalene (0.1), β-bisabolene (0.1), β-sesquiphellandrene (0.1), 1-nor-bourbonanone (0.1), viridiflorol (0.1), salvial-4(14)-en-1-one (0.1), 1,10-di-epi-cubenol (0.1), epi-α-muurolol (0.1), *cis*-calamenen-10-ol (0.1), α-bisabolol (0.1),	*Thymus munbyanus* (Jertil et Ziitra)	✓		✓		✓	Leaves and flowering aerial parts	[45]
24	2 E-Hexenol(0.1), α-Thujene (0.1), Thuja-2,4(10)-diene (0.1), 2-pentyl furan (0.1), α-Terpinene (0.1), E-β-Ocimene (0.1), E-linalool oxide (0.1), Terpinolene (0.1), p-cymenene (0.1), E-sabinene hydrate (0.1), E-Thujone (0.1), Camphor (0.1), Sabina ketone (0.1), p-Cymen-8-ol (0.1), Verbenone (0.1), Nerol (0.1), Z-carveol (0.1), Cumin aldehyde (0.1), neoiso-3-thujanol Acetate (0.1), E-sabinyl acetate (0.1), carvacrol (0.1), myrtenyl acetate (0.1), α-cubebene (0.1), β-elemene (0.1), α-Gurjunene (0.1), E-β-ionone (0.1), α-Cadinene (0.1), Longipinanol (0.1), Viridiflorol (0.1), mustakone (0.1), elemol acetate (0.1), Z-Thujopsenal (0.1), Mint sulfide (0.1), β-eudesmol acetate (0.1), 5E,9E-Farnesyl Acetone (0.1),	*Teucrium polium* (Khayatta ou Djaâda)				✓		Aerial pars, leaves	[46]

*1: cough; 2: Rhinitis; 3: Bronchitis; 4: Asthma; 5: Influenza, Flu; * Some of characteristics and properties of medicinal plants are extracted from Quezel and Santa [47] and IUCN [48].

2.2. Molecular Docking

All studied compounds were obtained from chemical structure databases ChemSpider (An Online Chemical Information Resource) [49]. Molecular docking carried out to determine binding affinity and predict the intermolecular interactions of molecules in receptors. We performed a docking of studied compounds in the binding pocket of SARS-CoV-2 main protease (pdb code 6LU7) [50].

The docking study was carried out with two programs; Autodock vina [51] and Autodock tools 1.5.6 [52]. such programs are usually used to dock known substrates into the active site or known protein-binding molecules to the surface of the model [53]. The crystallographic structure of SARS-CoV-2 main protease (pdb code 6LU7) is imported into "work space" of Discovery Studio 2016 program [54] to obtain the binding site [55]. The center of the active site has been determined and it corresponds to the coordinates: x= -10.782, y = 15.787 and z=71.277 on the basis of the co-crystallized bound peptidomimetic ligand [56]. The grid size was set at 20×20×20 xyz points with a grid spacing of 1 Å to cover the folic acid binding site in the enzyme and was generated by using the co-crystallized ligand (N3) as the center for docking [56]. For ligand and enzyme preparations; an extended PDB format, termed PDBQT, is used for coordinate files, which includes atomic partial charges and atom types. Torsion angles were calculated to assign the flexible and non-bonded rotation of molecules. The results were subsequently analyzed using Discovery studio 2016 [54].

2.3. Lipinski's Rule and ADMET Prediction

The Lipinski's rule and ADMET [57] parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) of potential inhibitors were calculated using pkCSM [58] and Swissadmet [59] web servers. The Lipinski's rule including; molecular weight, logP, number of rotatable bonds, number of hydrogen bonds acceptor and number hydrogen bonds donor were determinate. Molecules violating more than one of these parameters may have problems with bioavailability and a high probability of failure to display drug-likeness [60].

3. RESULTS AND DISCUSSIONS

3.1. Molecular Docking

Molecular docking was performed to find types of interactions and the binding affinity of studied molecules in the studied enzyme. 187 different natural compounds have been evaluated for their affinity against the SARS-CoV-2 main protease (pdb code 6LU7). The results are presented in Table 2.

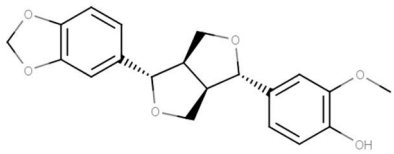
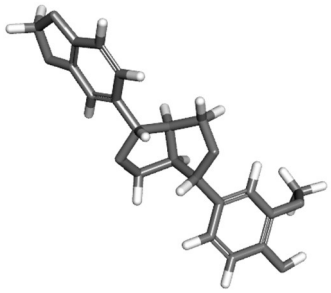
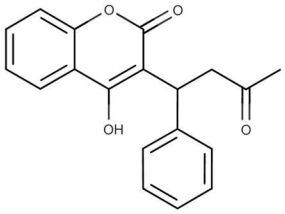
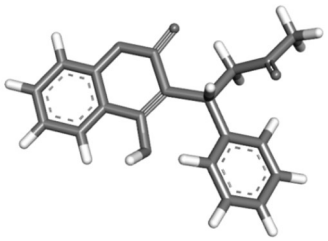
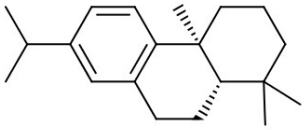
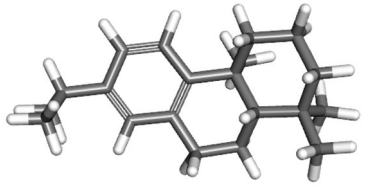
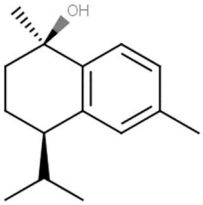
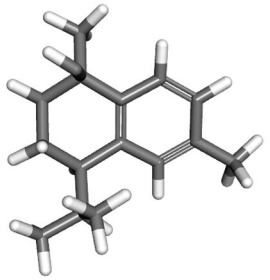
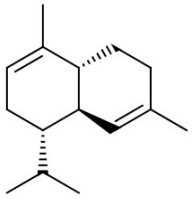
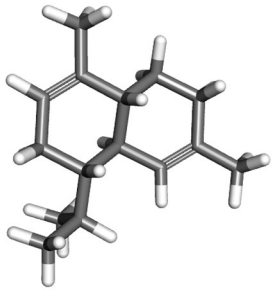
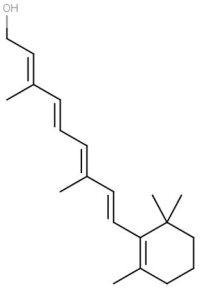
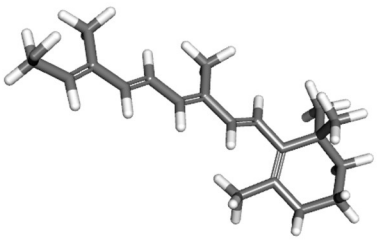
Table 2. Docking results: Affinity of the best conformation in the binding pocket of SARS-CoV-2 main protease.

N°	Name of molecules	Affinity (Kcal/mol)	N°	Name of molecules	Affinity (Kcal/mol)	N°	Name of molecules	Affinity (Kcal/mol)
1	α-Thujone	-4.9	**64**	**α-Cadinene**	**-6.1**	**127**	Camphore	-4.5
2	Perillaldehyde	-4.7	**65**	α-Thujene	-4.1	**128**	Naphtalene	-4.8
3	β-caryophyllene	-5.8	**66**	Linalool	-4.8	**129**	α-Pinene	-4.8
4	Perillyl alcohol	-4.8	**67**	α-Cubebene	-5.6	**130**	Isopulegol	-4.5
5	3,4-dimethylcinnoline	-5.5	**68**	α-Gurjunene	-5.3	**131**	Octane-3-one	-3.9
6	α-copaene	-5.1	**69**	E-caryophyllene	-5.2	**132**	Thymoquinone	-5.0
7	Limonene	-4.5	**70**	β-Gurjunene	-5.5	**133**	Eugenol	-4.9
8	6,8-Nonadien-2-one, 6-methyl-5-(1-methylethylidene)-	-5.0	**71**	Cadina-1,4-diene	-5.6	**134**	Trans-carvyl acetate	-5.1
9	γ -Muurolene	-5.3	**72**	Trans-Nerolidol	-5.2	**135**	Ylangene	-5.3
10	α-Zingiberene	-5.6	**73**	**Abietatriene**	**-6.4**	**136**	Cis-jasmone	-4.8
11	Methyl p-tert-butylphenyl acetate	-5.5	**74**	α-amorphene	-5.3	**137**	α-Muurolene	-5.4
12	(E)-3-Octadecene	-4.2	**75**	Tridecanal	-4.2	**138**	Viridiflorol	-5.8
13	(E)-Salvene	-4.3	**76**	β-Eudesmol	-5.7	**139**	Ledol	-5.3

14	Cis-verbenol	-4.4	**77**	Hexanal	-3.3	**140**	p-Cymene	-4.6
15	Borneol	-4.3	**78**	Octan-3-ol	-3.8	**141**	1-Octen-3-ylacetate	-4.0
16	Thymol	-4.7	**79**	6-Methyl-hepta-3,5-dien-2-one	-4.6	**142**	(3R)-3-Octanyl acetate	-4.1
17	Z-β-Damascenone	-4.9	**80**	Terpinene-4-ol	-4.7	**143**	Carvone	-4.8
18	Aromadendrene	-5.3	**81**	Elemol	-5.1	**144**	Lavandulyl acetate	-4.9
19	δ-cadinene	-5.8	**82**	Megastigmatrienone	-5.3	**145**	Myrtenyl acetate	-5.0
20	Spathulenol	-5.8	**83**	Ethyldibenzothiophene	-5.7	**146**	Neo-Allo-Ocimene	-4.7
21	Caryophyllene oxide	-5.5	**84**	Hexane	-3.0	**147**	n-Octyl acetate	-4.1
22	(z)-Tetradec-9-enoic acid	-4.4	**85**	4-Heptanal	-3.7	**148**	α-Bergamotene	-5.0
23	(E)-Tetradec-9-enoic acid	-5.0	**86**	Trans-Linalool oxide	-5.0	**149**	Bicyclogermacrene	-5.0
24	Methyl hexadecanoate	-4.3	**87**	Dihydropseudoionone	-5.2	**150**	γ-Eudesmol	-5.7
25	Ethylheptadecanoate	-5.0	**88**	Ethyllinoleate	-4.6	**151**	1-Octen-3-ol	-3.8
26	Tricosane	-4.1	**89**	n-Tricosane	-4.0	**152**	Benzene acetaldehyde	-4.2
27	Tetracosane	-4.3	**90**	3-Carene	-4.5	**153**	1-nonen-3-ol	-4.1
28	Hexacos-9-ene	-4.5	**91**	Methyl perillate	-4.9	**154**	p-mentha-2,4(8)-diene	-5.0
29	Hexacosane	-4.5	**92**	Perilla alcohol	-4.7	**155**	Myrtenol	-5.0
30	Benzene	-3.4	**93**			**156**	Trans-dihydrocarvone	-4.8
31	Cyclohexane	-3.2	**94**	Bornyl acetate	-5.2	**157**	Verbenone	-5.1
32	2,3-Butanediol	-3.8	**95**	β-Guaiene	-5.3	**158**	Carvacrol methyl ether	-5.0
33	Cis-2-Hexenal	-3.6	**96**	Trans-Calamenene	-5.9	**159**	β-cubebene	-5.6
34	3-Hexen-1-ol	-3.5	**97**	Spathlenol	-5.6	**160**	γ-himachalene	-5.4
35	1-Hexanol	-3.5	**98**	Farnesol	-5.4	**161**	β-Bisabolene	-5.6
36	Nonanal	-3.9	**99**	3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)-, acetate	-4.7	**162**	β-sesquiphellandrene	-5.9
37	Camphene	-4.0	**100**	4-Pyridinamine	-3.7	**163**	1-nor-bourbonanone	-5.3
38	β-pinene	-4.6	**101**	Aspartic acid	-4.7	**164**	salvial-4(14)-en-1-one	-5.1
39	Myrcene	-4.0	**102**	Phenol, 4-(2-aminopropyl)-	-4.8	**165**	1,10-di-epi-cubenol	-5.7
40	γ-terpinene	-4.6	**103**	Phenol, 2-methoxy-4-(1-propenyl)-, (E)-	-5.2	**166**	α-epi-muurolol	-5.7
41	Carvenone	-4.8	**104**	**Retinol**	**-6.1**	**167**	**cis-calamenen-10-ol**	**-6.3**
42	Pinocarvone	-4.9	**105**	**Warfarin**	**-7.1**	**168**	α-bisabolol	-5.8
43	Terpinen-4-ol	-4.3	**106**	β-Myrcene	-4.8	**169**	2 E-Hexenol	-3.6
44	Allo-aromadendrene	-5.4	**107**	α-Terpinene	-4.6	**170**	2-pentyl furan	-4.1
45	α-Terpineol	-4.8	**108**	Methyl citronellate	-4.6	**171**	(E)-β-ocimene	-4.5
46	δ-Terpineol	-5.2	**109**	Exo-2-hydroxycineole acetate	-5.2	**172**	E-linalool oxide	-5.0
47	p-Mentha-1 (7),8-dien-2-ol	-5.0	**110**	(E)-Methyl isoeugenol	-5.0	**173**	p-cymenene	-4.5
48	p-Cymen-8-ol	-5.0	**111**	γ-Elemene	-4.9	**174**	E-sabinene hydrate acetate	-4.9
49	Trans-Carveol	-4.7	**112**	Cubenol	-5.4	**175**	E-Thujone	-4.6
50	**Piperitol**	**-7.7**	**113**	Thuja-2,4(10)-diene	-4.5	**176**	Nerol	-4.8
51	Epi-Globulol	-5.3	**114**	Terpinolene	-4.9	**177**	Z-carveol	-4.6
52	Globulol	-5.6	**115**	Nopinone	-4.5	**178**	Cumin aldehyde	-4.8
53	α-Eudesmol	-5.6	**116**	Sabina ketone	-4.5	**179**	E-sabinyl acetate	-5.1
54	Sabinene	-4.4	**117**	Carvacrol acetate	-5.4	**180**	E-β-ionone	-5.2
55	Phenylethyl alcohol	-4.3	**118**	α-elemene	-5.6	**181**	E-Longipinanol	-5.5
56	Indole	-4.4	**119**	β-Copaene	-5.4	**182**	Mustakone	-5.8
57	β-bourbonene	-5.3	**120**	α-Guaiene	-5.7	**183**	Elemol acetate	-5.4
58	β-elemene	-4.9	**121**	Trans-β-Elemenone	-5.4	**184**	Thujopsenal	-5.4
59	α-humulene	-5.7	**122**	α-phellandrene	-4.7	**185**	Mintsulfide	-5.2
60	Trans-β-Farnesene	-5.2	**123**	(Z)-β-ocimene	-4.1	**186**	β-eudesmol acetate	-5.9
61	β-Ionone	-5.2	**124**	Allo-ocimene	-4.4	**187**	5E,9E-Farnesyl Acetone	-4.5
62	Germacrene D	-5.5	**125**	Carvacrol	-4.9	**Chloroquine**		-5.9
63	Pentadecane	-4.4	**126**	(Z)-Nerolidol	-5.2	**Hydroxychloroquine**		-6.6

The best energies of interaction with SARS-CoV-2 main protease are observed for Piperitol, Warfarin, Abietatriene, cis-calamenen-10-ol, α-Cadinene and Retinol (Table 3); so, these compounds could have more inhibitory potential against SARS-CoV-2 main protease than the other studied compounds.

Table 3. Structures with the best Affinity in the binding pocket of SARS-CoV-2 main protease.

N°	Name of molecules	Plant of origin	Affinity (Kcal/mol)	Structure 2D	Structure 3D
50	Piperitol	*Eucalyptus sp.*	**-7.7**		
105	Warfarin	*Glycyrrhiza glabra*	**-7.1**		
73	Abietatriene	*Juniperusoxycedrus L.*	**-6.4**		
167	Cis-calamenen-10-ol	*Thymus munbyanus*	**-6.3**		
64	α-Cadinene	*Marrubium vulgare L, Thymus numidicus Poiret and Teucrium polium*	**-6.1**		
104	Retinol	*Glycyrrhiza glabra*	**-6.1**		

The result of interactions between Piperitol and the studied enzyme (Figure 1) shows Conventional Hydrogen Bond with Gly 143 and Ser 144 residues, Carbon Hydrogen bonding with Phe 140 and Gln 189 residues and π-Alkyl with Cys 145, His 172 and His 163 residue.

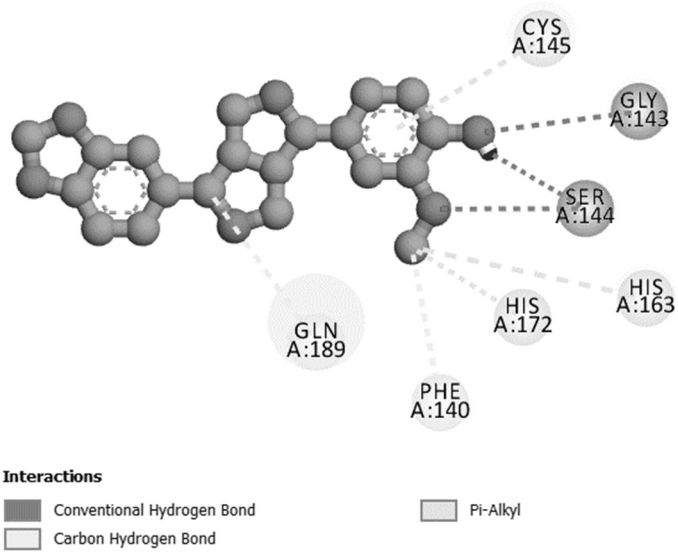


Figure 1: Interactions between Piperitol and SARS-CoV-2 main protease.

The presence of hydrogen bonding in the complex formed by Piperitol and the studied enzyme increase the affinity of the complex and gives to Piperitol a pharmacological importance; actually hydrogen bonds play a major role in the pharmacological effect of ligands [22, 61].

The result of interactions between Warfarin and the studied enzyme (Figure 2) shows Conventional Hydrogen Bond with Glu 166, Ser 144 and Cys 145 residues, π-π T-shaped with His 41 residue and π-Alkyl with Met 164 residue.

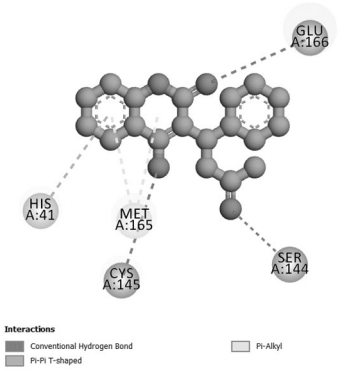


Figure 2: Interactions between Warfarin and SARS-CoV-2 main protease.

The affinity of Piperitol, Warfarin, Abietatriene, cis-calamenen-10-ol, α-Cadinene and Retinol in the binding pocket of the studied enzyme can be explained by the number and type of bonds noticed in formed complexes, indeed the presence of hydrogen bonds shows an important potential pharmacological effect, by the inhibition of SARS-CoV-2 main protease. The inhibition of this protein will induce the inhibition of viral replication; these results show that these molecules could be interesting in the clinical management of COVID-19.

3.2. Lipinski's Rule and ADMET Prediction

The Lipinski's rule and ADMET parameters of the selected compounds, the inhibitor (N3), chloroquine and hydroxychloroquine were calculated using pkCSM and Swissadmet web servers. The Lipinski's rule including logP, number of hydrogen bonds acceptor, number hydrogen bonds donor, number of rotatable bonds and molecular weight were shown in Table 4.

Table 4. Lipinski's rule of potential inhibitors, N3, chloroquine and hydroxychloroquine.

Compounds	Property					Lipinski violations
	Log P	H-bond Acceptor	H-bond Donor	Rotatable bonds	Molecular weight g/mol	
Rule	<4.15	≤10	<5	<10	≤500	≤1
Piperitol	1.57	6	1	3	356.37	0
Warfarin	2.51	4	1	4	308.33	0
Abietatriene	6.64	0	0	1	270.45	1
Cis-calamenen-10-ol	3.46	1	1	1	218.33	0
α-Cadinene	4.63	0	0	1	204.35	1
Retinol	4.48	1	1	5	286.45	1
N3	0.61	9	6	23	680.79	3
Chloroquine	3.20	2	1	8	319.87	0
Hydroxychloroquine	2.35	3	2	9	335.87	0

All the selected compounds respect the conditions mentioned in Lipinski's rule. The co-crystallized ligand presented three Lipinski Violations, whereas chloroquine and hydroxychloroquine respect all conditions of Lipinski's rule. The ADMET prediction was used in this work to calculate the pharmacokinetics parameters of selected compounds (Table 5).

Table 5. In silico ADMET prediction and synthetic accessibility values of selected compounds, chloroquine and hydroxychloroquine.

Comp.	Absorption		Distribution		Metabolism						Excretion		Synthetic accessibility
	Water solubility	Intestinal absorption (human)	Volume of distribution	Blood-brain barrier Permeability CYP	CYP450						Total clearance	hERG I inhibitor - hERG II inhibitor	
					2D6	3A4	1A2	2C19	2C9	2D6	3A4		
					Substrate		Inhibition						
	Numeric				Categorical						Numeric	Categorical	Numeric
	(log mol/l)	(% absorbed)	(log L/Kg)	(log BB)	(yes/No)						(log ml/ min/Kg)	(yes/ No)	
Piperitol	-3.975	97.647	-0.314	-0.265	No	Yes	Yes	Yes	Yes	No	0.053	No-No	4.19
Warfarin	-4.513	96.161	-0.266	-0.17	No	Yes	Yes	Yes	Yes	No	0.719	No-No	3.79
Abietatriene	-6.749	95.083	1.54	0.628	No	Yes	Yes	Yes	No	No	0.961	No-Yes	3.18
Cis-calamenen-10-ol	-4.13	92.95	0.868	0.215	No	Yes	Yes	No	No	No	1.161	No-No	2.84
α-Cadinene	-5.851	97.173	0.695	0.791	No	No	No	No	No	No	1.18	No-No	4.35
Retinol	-6.404	91.728	0.497	0.642	No	Yes	Yes	No	No	No	1.531	No-Yes	4.28
Chloroquine	-4.249	89.950	1.332	0.349	Yes	Yes	No	No	No	Yes	1.092	No-Yes	2.76
Hydroxychloroquine	-3.627	90.217	1.076	0.074	Yes	Yes	Yes	No	No	Yes	1.152	No-Yes	2.82

The results of ADMET analysis show that all the selected molecules have a low values for brain blood partition coefficient, were found indicating that they will have a very low potential to cross the brain-blood brain barrier thereby eliminating the possibility of CNS related toxicity. Additionally, the other pharmacokinetics parameters such as human intestinal absorption (HIA), water solubility (log mol/L), metabolism and Synthetic Accessibility are all acceptable. The toxicity indicated by predicted hERG I and hERG II inhibitors shows that all selected compounds show hERG inhibition properties except Abietatriene and Retinol, that present hERG II inhibition, as well as for chloroquine and hydroxychloroquine.

Piperitol, Warfarin, cis-calamenen-10-ol and α-Cadinene are the structures with best affinity in the binding site of the enzyme and all of them respect the conditions mentioned in Lipinski's rule and have acceptable ADMET proprieties; so, these compounds could have more potent antiviral treatment of COVID-19 than the studied compounds, and they have important pharmacokinetic properties and bioavailability than chloroquine and hydroxychloroquine.

4. CONCLUSION

In this study, we have tried to carry out a docking study of 187 natural compounds in the active site of SARS-Cov-2 main protease. The result indicates that Piperitol, Warfarin, cis-calamenen-10-ol, and α-Cadinene are the structures with best affinity in the binding site of the enzyme and all of them respect the conditions mentioned in Lipinski's rule and have acceptable ADMET proprieties; so, these compounds could have more potent antiviral treatment of COVID-19 than the studied compounds, and they have important pharmacokinetic properties and bioavailability than chloroquine and hydroxychloroquine. The synthesis of these molecules and the evaluation of their in vitro activity against COVID-19 could be interesting.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the author(s).

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