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Original Article

In-silico evaluation of the efficacy of essential oils from *Artemisia absinthium*, *Artemisia herba-alba*, and *Artemisia annua* against SARS-CoV-2

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Abstract

Since the outbreak of COVID-19 in China in December 2019, the pandemic has spread to almost every country in the world, resulting in more than half a billion sick patients and more than seven million victims. The objective of our present study is to explore some plant resources available in Algeria and to verify their potential use against SARS-CoV-2, involved in COVID-19. The study used plant species belonging to the genus Artemisia and growing naturally in Algeria: *Artemisia herba-alba* and *Artemisia absinthium*. The essential oils of these two species, analysed by GC-MS, gave a fairly rich chromatographic profile. The comparison of this profile was made with a Malagasy species: *Artemisia annua*. An in-silico study by molecular docking was conducted on the active molecules of the three species in order to predict their efficacy and possible toxicity. The target proteins of the molecular docking are three proteases: 6LU7, 6WUU, 7JRN and a receptor linked to ACE2: 6M0J. Our study shows that out of 55 molecules tested, 8 present in these 3 plants have a very strong potential to inhibit the proteins studied: Cubebene, Elemene, Mustakone, Azulol, Myrtenyl acetate, β-Selinene, Epi-α-Cadinol, and Germacrene D. We also notice that out of the 8 molecules selected, those extracted from *Artemisia absinthium* are the ones with the highest scores. This plant may therefore have a very high antiviral potential. Mixtures of the three plants could be complementary in their effectiveness. These findings suggest that the selected compounds warrant further experimental validation in vitro and in vivo.

Keywords: SRAS-CoV-2, Mpro, 6LU7, 6WUU, 7JRN, 6MOJ, Docking.

1. Introduction

COVID-19 is a disease caused by SARS-CoV-2 and poses a major threat to public health worldwide due to high infection and mortality rates [1]. Morbidity and mortality continue to increase due to the lack of a specific drug that prevents the progression of COVID-19, despite the presence of some vaccines. In the first half of 2022, several countries made a major effort to adapt to the consequences of the COVID-19 pandemic, including blocking the tourism and travel sector by isolating arrivals [2,3]. The first case of Coronavirus 2, severe acute respiratory syndrome (SARS-CoV-2), was reported on December 30th 2019 in Wuhan Province, China, and was declared a global pandemic with cough, fever and breathing difficulties as the main symptoms. These symptoms can progress to respiratory distress and organ failure. In addition, the disease can cause systemic inflammation. Transmission is by droplet infection, but other modes such as airborne and faecal-oral transmission are also speculated [4]. The alarming numbers of infected patient are causing all global health systems to focus on this pandemic. With 704,753,890 cases worldwide and 7,010,681 deaths as of April 13th 2024, this pandemic has the potential to capture the attention of physicians and researchers [1]. The emergence of new, rapidly transmissible variants of SARS-CoV-2 threatens to prolong this pandemic and could have devastating health and economic consequences. SARS-CoV-2 continues to spread throughout 2022. The disease remains under surveillance despite a declining case fatality rate over the past two years, but prevention and treatment of the virus remain a priority for scientists and the world. Containment, which is widely disputed, was part of the battery of procedures applied. Vaccines then took over to protect mainly the professional categories at the forefront but also the fragile

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social categories. World population had found itself isolated without specific medication before Didier Raoult's first protocols. Many patient therefore turned to traditional [5–8] and medicinal plants with recognized antiviral activity [9], including white mugwort (*Artemisia herba-alba*) and wormwood (*Artemisia absinthium*), nigella seeds (*Nigella sativa*)…etc. [10–12]. In some countries, such as Madagascar, President Andry Rajoelina has praised the miraculous virtues of an herbal tea made from mugwort (*Artemisia annua*). Unlike previous studies focusing on single species, our work compares three *Artemisia* species and evaluates their bioactive compounds across four SARS-CoV-2 targets with in-silico ADME/Tox analysis. This is what we will try to elucidate through our research concerning the effectiveness and efficacy of the extracts of these three plants of the genus Artemisia: *Artemisia herba-alba*, *Artemisia absinthium* and *Artemisia annua*, on the receptor proteins of the coronavirus.

2. Material and methods

2.1. Biological material

2.1.1. Artemisia herba alba

The sample of white mugwort was collected in March in the Ouenza region of Souk-Ahras. The species was identified by Prof. Hadef Youcef at the Faculty of Medicine. The plants were dried for a fortnight at room temperature on kraft paper and in the shade. After drying, the plants were crumbled before being subjected to hydrodistillation by Clevenger [13]. After three hours of extraction, the essential oil was stored and preserved in a tightly closed glass bottle and stored in the dark for fine chemical analysis by GC-MS.

2.1.2. Artemisia absinthium

The wormwood sample was collected in April in the Annaba region. The species was identified by Professor Zaafour Moncef at the Department of Biology. The plants were dried for a fortnight at room temperature on kraft paper and in the shade. After drying, the plants were crumbled before being subjected to hydrodistillation by Clevenger. After three hours of extraction, the essential oil was stored and preserved in a tightly closed glass bottle and kept in the dark for fine chemical analysis by GC-MS.

2.1.3. Artemisia annua

As no fresh *A. annua* samples were available, we relied on GC-MS data from [14], a validated reference source, acknowledging this as a study limitation. The authors proceeded in the same way with the harvesting, drying, extraction of the essential oil and finally the fine analysis by GC-MS.

2.1.4. GC-MS analysis

Gas chromatography-mass spectrometry was used for qualitative and quantitative analysis. The apparatus used is PerkinElmer GC-MS type and under electron impact ionisation at 70 ev. DB5 column (30m; film thickness diameter 1µm) with 5% of diphenylmethylsilicone was used. A splitless injection mode is used. The initial temperature was maintained at 60°C for 1 min, then increased by 3°C/min to reach 200°C. The injector and detector temperatures are 250°C and 285°C respectively. Helium was used as the carrier gas with a flow rate of 1 ml/min. The standard solutions and essential oils were diluted in absolute alcohol (1 g/l). The identification of the compounds was done by comparing the retention times of the samples with those of the standard solutions, and then by comparing the mass spectra with those contained in the NIST libraries, the percentage of each compound being calculated by the internal standardisation method.

2.2. In-silico study

2.2.1. Protein selection and preparation

The protein selection was conducted following the method described by [15]. The 3D structures of all chemical compounds were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The main protease protein targeted was 6lu7 enzyme. Downloaded structures were prepared prior to docking as fellow: PyMOL software was used to visualize, to remove hetatoms and to keep only Chain A, then to convert sdf files to pdb format. Hydrogen bonds structures were optimized and atoms in missing loops or side chains were added. Water molecules were removed and files were saved as PDB file format.

2.2.2. Ligand preparation

Structures of our ligands were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and saved in SDF format. Files were converted from SDF to PDB format using PyMOL.

2.2.3. Docking protocol

Docking grid was defined around the N3 inhibitor binding site (Mpro) with grid size 30×30×30 Å, spacing 0.5 Å, centered at active pocket coordinates. To conduct molecular docking, we selected the binding site of inhibitor N3 as a binding cavity. Docking sites targeted for 6LU7 are: x = -17.497; y = 12.937; z = 64.063, at grid spacing of 0.500 Angstrom.Virtual screening was carried our using AutoDockVina and the best ligand/protein mode was identified based on the binding energy. The scoring function of AutoDockVina is: $C=\sum i<jftitj(rij)$, where the summation is over all of the pairs of atoms that can move relative to each other, normally excluding 1–4 interactions, i.e. atoms separated by 3 consecutive covalent bonds. Here, each atom *i* is assigned a type *ti*, and a symmetric set of interaction functions *ftitj* of the interatomic distance *rij* should be defined.

2.3. Data

Figures 1; 2; 3 and **4** show the PDB ID, resolution and description of COVID-19 main protease selected for this study. PDB ID, resolution and description of COVID-19 main protease (https://pubchem.ncbi.nlm.nih.gov)

2.4. *In Silico* prediction of physicochemical and toxicological behavior of assessed ligands

Physicochemical and Toxicological studies were conducted under SwissADME online software and Molinspiration online software. The SMILES structures of ligands were obtained from PubChem database. The softwares allow us to compute and predict ADME parameters (Absorption, Distribution, Metabolism & Excretion), pharmacokinetic properties, “druglike” nature and medicinal chemistry friendliness of molecules, but do not predict if a compound is pharmacologically active. This response is estimated by molecular docking. Simulation of physicochemical and toxicological behavior of our ligands was

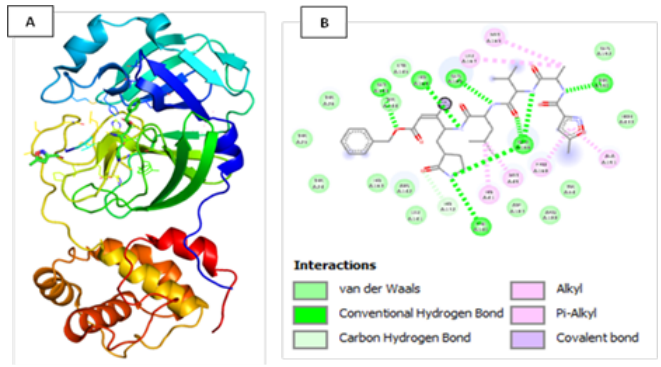


Fig. 1. Representation of the structure of the main protease of COVID-19 (Mpro) in complex with an N3 inhibitor. Legend: (A)- Crystal structure of the main protease COVID-19 in complex with an N3 inhibitor. (B) 2D interaction of peptide like N3 inhibitor with amino acid residues of COVID-19 Mpro.

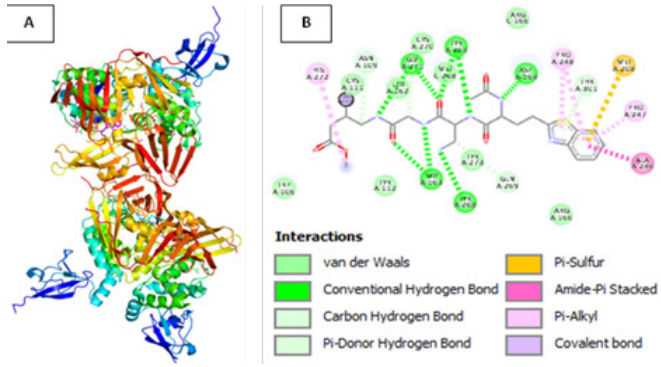


Fig. 2. Structure of the SARS CoV-2 papain protease in complex with the peptide inhibitor VIR250. Legend: (A)- Crystal structure of the SARS CoV-2 papain-like protease in complex with the peptide inhibitor VIR250. (B) 2D interaction of the peptide like inhibitor VIR250 with the amino acid residues.

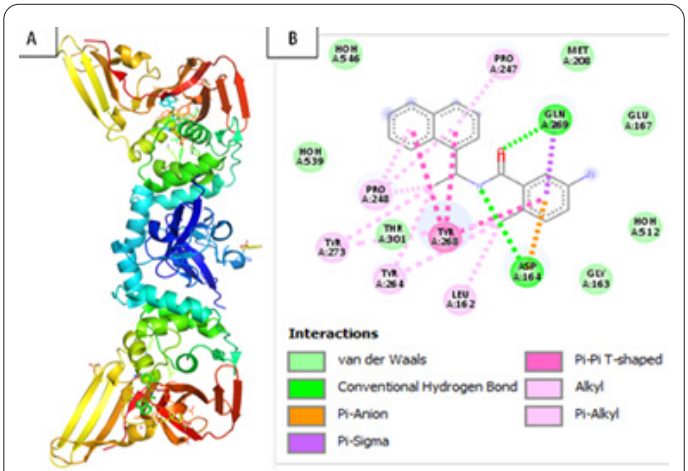


Fig. 3. Structure of the wild-type papain protease SARS-CoV-2 (PLPro) with inhibitor GRL0617. Legend: (A)- Crystal structure of the wild-type papain protease SARS-CoV-2 (PLPro) with inhibitor GRL0617. (B)2D interaction of the peptide like inhibitor GRL0617 with the amino acid residues.

obtained from SwissADME developed by the Molecular Modeling Group from the Swiss Institute of Bioinformatics (www.swissadme.ch/index.php). The parameters obtained were: Molecular Weight (g/mol); H-bond donors; H-bond acceptors; Lipophilicity Log Po/w; Water solubility

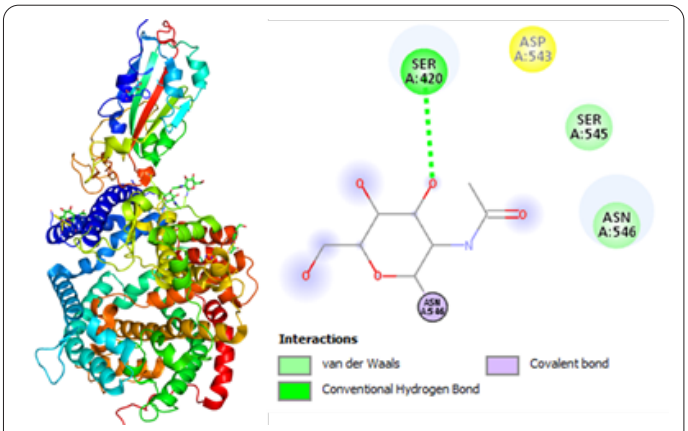


Fig. 4. Representation of the crystal structure of the ACE2-linked SARS-CoV-2 peak receptor binding domain. Legend: (A) Crystal structure of the ACE2-linked SARS-CoV-2 spike receptor binding domain. (B) 2D interaction of the peptide as inhibitor with the amino acid residues.

(Log S); Molar Refractivity; Blood-Brain-Barrier (BBB) permeability; Gastro Intestinal (GI) absorption; Skin permeation. Predicted bioactivity parameters were completed from Molinspiration developed by Bratislava University (https://www.molinspiration.com/). The parameters obtained were: G Protein-Coupled Receptor (GPCR) ligand; Ion channel modulator; Kinase inhibitor; Nuclear receptor ligand; Protease inhibitor; Enzyme inhibitor. Although SwissADME and Molinspiration are reliable for early-stage screening, they do not replace experimental pharmacokinetic or toxicological testing. Therefore, predictions should be interpreted cautiously.

3. Results

We already notice that the three essential oils are different in terms of qualitative composition. Only Caryophyllene is finally common to all three species. Elemene, Cis-Jasmone, Thujone, Chrysanthenone, Iso-Chrysanthenone, Myrcene, cis-Verbenol, Sabinene and Pinene are present in *Artemisia herba-alba* species and absent in the other two species. Mustakone, Azulol, Copaborneol, Myrtenylacetate, Spathulenol, τ-Muurolol, Epicubebol, β-Guaiene, Aromadendreneoxide, Linalool, D-Carvone, o-Cymene, p-Cymen-8-ol, 3-Carene, Linalooloxide, Bornylacetate, D-Limonene, Fenchone, Dehydrosabinen, Eucalyptol and Endo-Borneol are present in *Artemisia absinthium* species and are absent in the other two species. β-selinene, Germacrene, G-cadinene, Epi-α-cadinol, Pinocarveylacetate, Germacrene D, Myrtenal, Artemisia alcohol, Trans-pinocarveol, 1,8-cineole are present in *Artemisia annua* species and absent in the other two species.

3.1. Molecular docking results

The following table shows the results of the molecular docking of each molecule found in the essential oils of the three species.

From this table we can see that for 6WUU the maximum value is Δ= -6.0 of β-selinene and the minimum value is Δ= -4.1 of Tricyclene and Borneol.

For 6LU7 the maximum value is Δ=-6.4 from Epi-α-cadinol and the minimum value is Δ=-3.9 from Myrcene.

For 7JRN the maximum value is Δ=-8.0 of Azulol and the minimum value is Δ=-4.7 of Borneol.

For 6M0J the maximum value is Δ=-6.4 of Copabor-

Table 1. Raw molecular docking data for the essential oils studied.

Molecules	6WUU	6LU7	7JRN	6M0J	*Total*
β-selinene	**-6.0**	-5.4	-7.4	-6.2	**-25,0**
α-copaene	-5.9	-5.6	-7.3	-6.3	**-25,1**
Mustakone	-5.9	-5.3	-7.3	-6.3	-24,8
Cubebene	-5.8	-5.6	-6.8	-6.1	-24,3
Azulol	-5.8	-6.1	**-8.0**	-6.1	**-26,0**
Germacrene A	-5.8	-5.3	-6.9	-6.1	-24,1
Copaborneol	-5.8	-5.4	-6.7	**-6.4**	-24,3
Myrtenylacetate	-5.8	-5.6	-7.7	**-6.4**	**-25,5**
Spathulenol	-5.8	-5.6	-7.5	**-6.4**	**-25,3**
τ-Muurolol	-5.8	-5.6	-6.7	-6.0	-24,1
Bicyclogermacrene	-5.7	-5.2	-6.2	-6.2	-23,3
Caryophyllene	-5.7	-5.1	-6.8	-6.0	-23,6
Epicubebol	-5.7	-5.6	-6.5	-5.9	-23,7
G-cadinene	-5.7	-5.7	-7.0	-6.0	-24,4
Epi-α-cadinol	-5.5	**-6.4**	-7.0	-5.9	-24,8
Pinocarveylacetate	-5.5	-5.0	-5.5	-5.7	-21,7
β-Guaiene	-5.5	-5.5	-7.2	-6.3	-24,5
Aromadendreneoxide	-5.5	-5.3	-6.6	-5.9	-23,3
Germacrene D	-5.4	-5.3	-6.8	**-6.4**	-23,9
Carveol	-5.3	-4.9	-6.1	-5.3	-21,6
Elemene	-5.3	-5.2	-6.9	-6.1	-23,5
Pinocarvone	-5.2	-4.7	-5.9	-5.8	-21,6
Linalool	-5.2	-4.4	-5.6	-4.9	-20,1
D-Carvone	-5.2	-4.6	-6.4	-5.3	-21,5
o-Cymene	-5.1	-4.3	-5.7	-4.9	-20,0
p-Cymen-8-ol	-5.1	-4.9	-6.3	-5.3	-21,6
Cis-Jasmone	-5.0	-4.5	-6.2	-5.7	-21,4
Thujone	-5.0	-4.7	-6.1	-5.7	-21,5
3-Carene	-5.0	-4.5	-5.8	-5.2	-20,5
Linalooloxide	-5.0	-4.9	-5.6	-4.9	-20,4
Myrtenal	-5.0	-4.4	-5.8	-5.2	-20,4
Bornylacetate	-5.0	-5.3	-5.4	-5.6	-21,3
D-Limonene	-4.9	-4.4	-6.1	-5.1	-20,5
L-α-Terpineol	-4.9	-4.7	-6.4	-5.1	-21,1
Terpinen-4-ol	-4.9	-4.4	-6.5	-5.0	-20,8
Verbenone	-4.9	-4.5	-6.0	-5.3	-20,7
Myrtenol	-4.8	-4.9	-5.7	-5.0	-20,4
Chrysanthenone	-4.7	-4.6	-5.7	-5.1	-20,1
Iso-Chrysanthenone	-4.7	-4.5	-5.7	-5.1	-20,0
Myrcene	-4.7	-3.9	-5.9	-5.1	-19,6
cis-Verbenol	-4.7	-4.8	-6.2	-5.2	-20,9
Artemisia alcohol	-4.6	-4.0	-5.9	-5.0	-19,5
Trans-pinocarveol	-4.6	-4.6	-5.3	-5.3	-19,8
Fenchone	-4.6	-4.5	-5.9	-5.4	-20,4
Dehydrosabinen	-4.6	-4.5	-5.6	-4.9	-19,6
1,8-cineole	-4.5	-4.2	-5.7	-5.2	-19,6
Eucalyptol	-4.5	-4.2	-5.7	-5.1	-19,5
Sabinene	-4.5	-4.4	-5.3	-5.0	-19,2
Pinene	-4.5	-4.2	-5.7	-5.1	-19,5
Camphor	-4.4	-4.4	-5.3	-5.1	-19,2
Artemisia ketone	-4.4	-4.3	-5.7	-5.1	-19,5
Endo-Borneol	-4.4	-4.3	-5.1	-5.1	-18,9
Camphene	-4.4	-3.9	-5.6	-5.3	-19,2
Borneol	-4.1	-4.3	-4.7	-5.1	-18,2
Tricyclene	-4.1	-4.0	-5.7	-5.2	-19,0

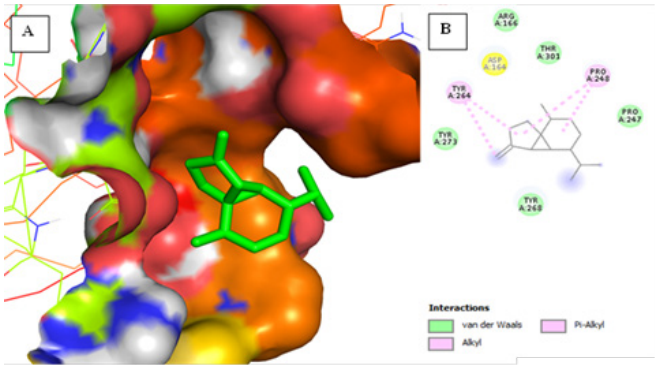


Fig. 5. (A) 3D structure of the 6WUU active site with Cubebene best mode (B) Amino acids involved in the binding site.

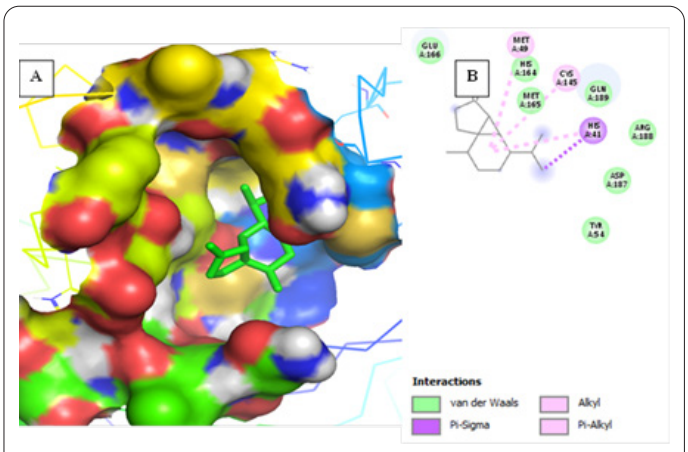


Fig. 6. (A) 3D structure of the 6LU7 active site with Cubebene best mode (B) Amino acids involved in the binding site.

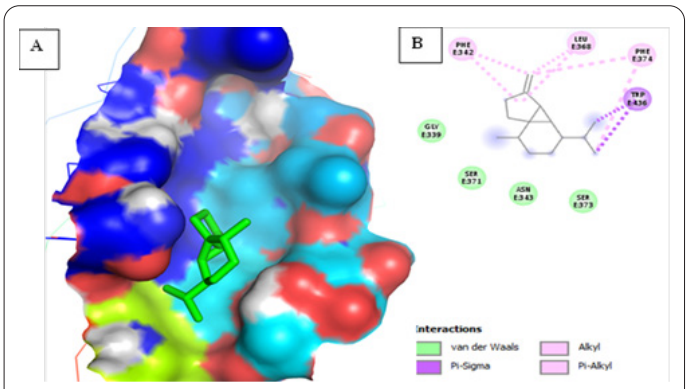


Fig. 7. (A) 3D structure of the 6M0J active site with Cubebene best mode (B) Amino acids involved in the binding site.

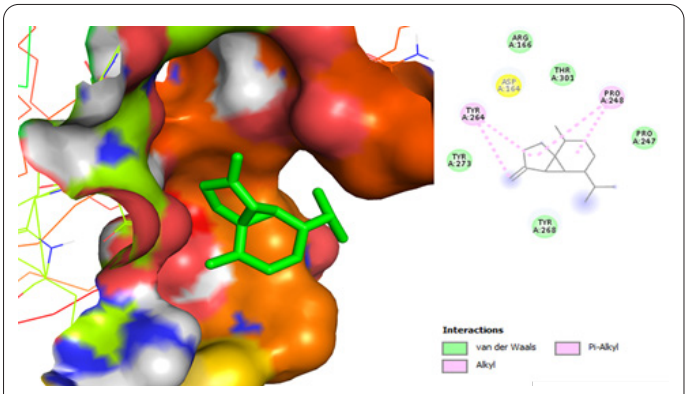


Fig. 8. (A) 3D structure of the 7JRN active site with Elemene best mode (B) Amino acids involved in the binding site.

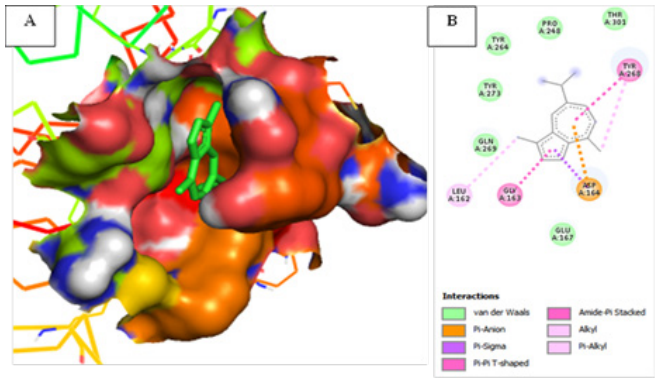


Fig. 9. (A) 3D structure of the 7JRN active site with Azulol best mode. (B) Amino acids involved in the binding site.

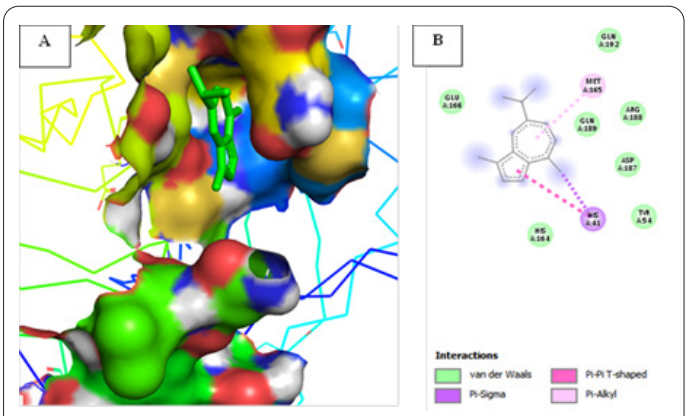


Fig. 11. (A) 3D structure of the 6LU7 active site with Azulol best mode. (B) Amino acids involved in the binding site.

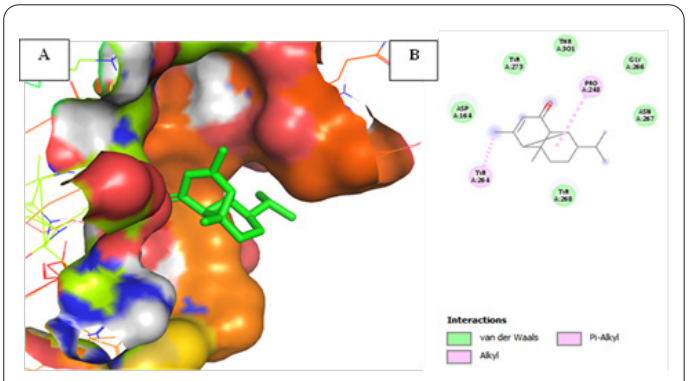


Fig. 12. (A) 3D structure of the 6WUU active site with best mode Mustakone (B) Amino acids involved in the binding site.

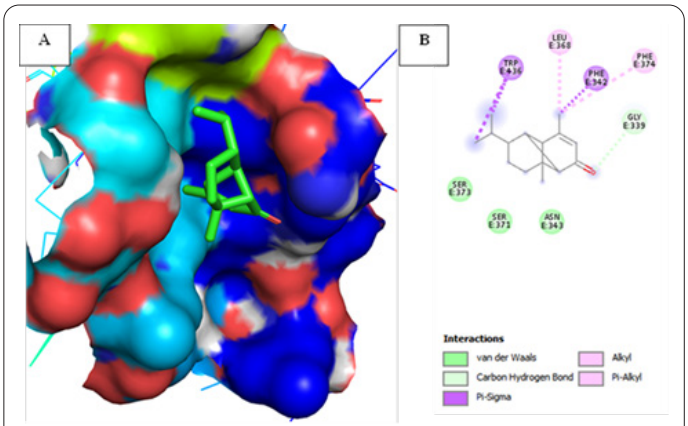


Fig. 13. (A) 3D structure of the 6M0J active site with Myrtenyl acetate best mode (B) Amino acids involved in the binding site.

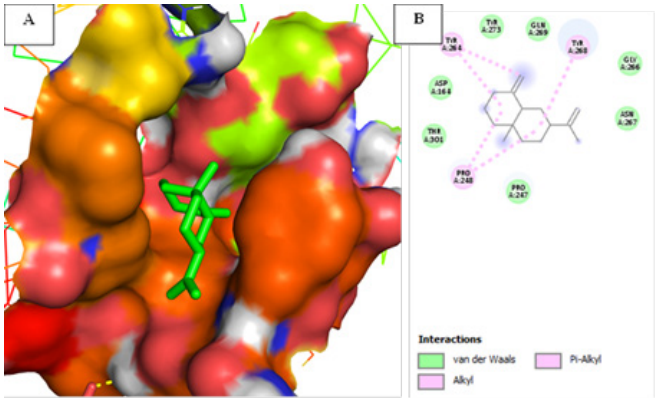


Fig. 14. (A) 3D structure of the 7JRN active site with β-Selinene best mode (B) Amino acids involved in the binding site.

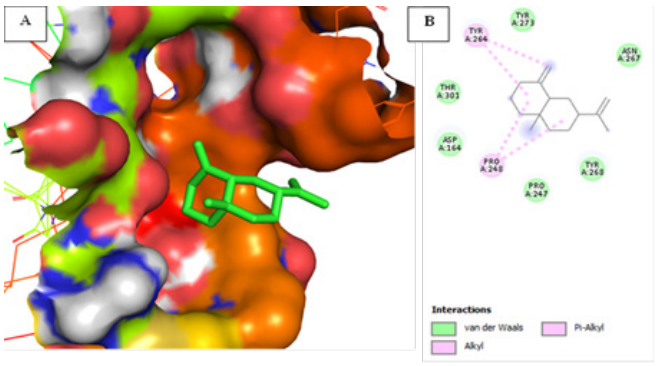


Fig. 15. (A) 3D structure of the 6WUU active site with β-Selinene best mode (B) Amino acids involved in the binding site.

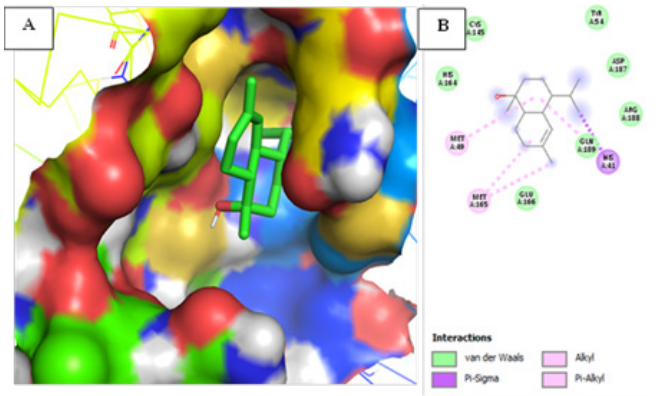


Fig. 16. (A) 3D structure of the 6LU7 active site with Epi-α-Cadinol best mode (B) Amino acids involved in the binding site.

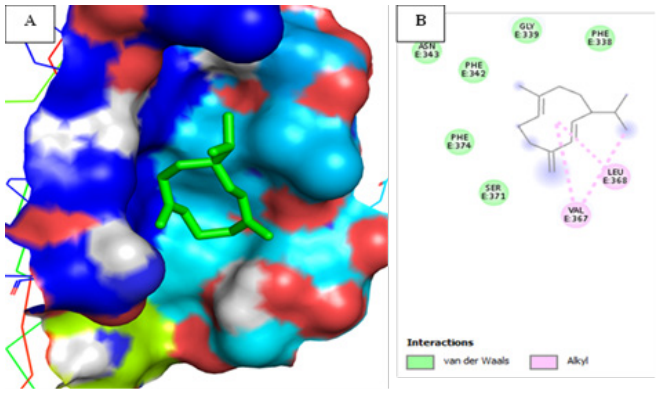


Fig. 17. ((A) 3D structure of the 6M0J active site with Germacrene D best mode.

neol, Myrtenylacetate and Spathulenol and the minimum value is Δ= -4.9 of Linalool, Dehydrosabinen, o-Cymene, Linalooloxide.

3.2. Toxicological study

The simulation of the physicochemical and toxicological behaviour of our ligands by ADME allows us to obtain results on: molecular weight (g/mol), H-bond donors, H-bond acceptors, Lipophilicity (Log Po/w), Solubility in water (Log S), as well as pharmacokinetics: gastrointestinal absorption, BBB permeability, skin permeability (cm/s) and drug-likeness (Lipinski). According to the results obtained, the studied molecules comply with the Lipinski rule [16], which allows their safe human consumption and their use as remedies against viral diseases or for the development of drugs based on these compounds.

3.3. Antiviral *in silico* study

This simulation provides the predicted percentage inhibition of compounds in specific viruses:

- Human Immunodeficiency Virus (HIV);
- Hepatitis C Virus (HCV);
- Hepatitis B virus (HBV);
- Human herpes virus (HHV).

4. Discussion

The most interesting antiviral predictive activities are those of Azulol with two maximum scores for HBV and HIV. Myrtenyl acetate comes next with a maximum value for HCV. Mustakone occupies the third position with an interesting value against HHV. We note that out of the eight molecules selected, those extracted from *Artemisia absinthium* are the ones with the highest scores. This plant, known for its large biological activities, may therefore have a very high antiviral potential [16,17].

According to the results of the in-silico evaluation of the antiviral activity of the selected molecules (Table 1). Azulol presents a very important activity against HIV with a percentage of inhibition of 77%, this result is very encouraging in terms of research of molecules biologically active against HIV, so Azulol presents a significant inhibitory power against HBV compared to other molecules. Myrtenyl acetate shows a high percentage of inhibition (67%) against HCV compared to the other molecules in this study. Mustakone showed a percentage of inhibition (41%) against HHV. According to the in silico results, Cubebene, Elemene, Azulol, Mustakone, Myrtenyl acetate, β-Selinene, Epi-α-Cadinol, and Germacrene-D have better affinity against the main proteins of COVİD-19 (Mpro; PLpro; 6M0J; 7JRN). These molecules are present in some of the three Artemisia plants studied (*Artemisia herba-alba*, *Artemisia absinthium* and *Artemisia annua*), at different levels. *Artemisia herba-alba* exhibits a wide range of biological activities; antibacterial [18], antioxidant [18], antileishmanial [19]. This plant has an excellent antimicrobial effect [20]. White mugwort has major components like Cubebene and Elemene. This plant has provided two promising molecules, one of which is in common with annual mugwort (Table 1). *Artemisia absinthium* exhibits its biological activities, such as hypoglycaemic agents, antioxidants and anti-inflammatory [21], antifungal [22]. Wormwood has major components like Mustakone, Azulol and Myrtenyl acetate. These three molecules happen to be the most promising in terms of antiviral activities

(Table 2) and make this species a major component to be included in future treatments. *Artemisia annua* has several biological activities, antimalarial [23], anti-tumour [24], and has antibacterial, antifungal [25]. The annual has major components like β-Selinene, Epi-α-Cadinol and Germacrene D. This plant is strongly justified in its use against COVID-19, as four out of the eight selected molecules are present, three of which are specific to it. However, these four molecules are not the ones with the highest scores in the antiviral prediction study (Table 2). Cubebene has a wide range of biological activities, including antimicrobial activity [26]. Elemene has antifungal [27] and antibacterial activity [28]. Azulol has antimicrobial and anti-inflammatory activity [29]. Mustakone has antibacterial and antiplasmodial activity [30]. Myrtenyl acetate exhibits antimicrobial activity [26], antifungal activities [31] and antileshmanial activities [32]. β-selinene exhibits antioxidant (Mayachiew and Devahastin, 2008), antimicrobial and anti-inflammatory activities [33]. Epi-α-cadinol has antibacterial, antimicrobial [34], anti-inflammatory and antispasmodic activities [35]. Germacrene-D has antioxidant activity [36] and antibacterial activity [37]. These compounds may serve as potential scaffolds for future antiviral drug development, pending further experimental validation.

The spread of the COVID-19 epidemic has challenged the health sector worldwide. Major failures are noted in high GDP countries, where the health sector was far ahead of the rest of the world. The emergence of new viruses is therefore challenging health systems around the world. The urgency of the response is causing teams of doctors and researchers around the world to look for quick and effective solutions. To contribute to this fight against COVID-19, a molecular docking based on virtual screening was carried out to identify new compounds with the potential to bind to the main COVID-19 proteins. Three promising species belonging to the genus Artemisia (*Artemisia herba-alba*, *Artemisia absinthium* and *Artemisia annua*), were explored and the chemical composition of these three species was used in the in-silico study. The essential oils, which are very rich in bioactive molecules, allowed an inventory of 55 molecules differentially shared between the three species; *Artemisia herba-alba*; *Artemisia absinthium* and *Artemisia annua*. Cubebene, Elemene, Azulol, Mustakone, Myrtenyl acetate, β-Selinene, Epi-α-Cadinol and Germacrene-D have a better binding affinity to the four coronavirus proteins: Mpro; PLpro; 6M0J and 7JRN. The selected molecules show promising binding affinities, but further experimental and clinical studies are required to confirm their antiviral potential.

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Table 2. *In-silico* evaluation of the antiviral activity of the selected molecules.

Molecules	VHB	VHC	HHV	VIH
Cubebene[1, 3]	16.102	51.062	29.151	56.918
Elemene[1]	8.469	55.114	33.747	60.597
Mustakone[2]	10.529	41.778	**41.833**	48.419
Azulol[2]	**21.811**	30.647	25.657	**77.195**
Myrtenyl acetate[2]	13.237	**67.134**	25.979	57.015
β-Selinene[3]	13.613	55.248	33.74	59.681
Epi-α-Cadinol[3]	3.538	23.903	35.954	42.278
Germacrene D[3]	16.425	45.106	30.066	65.791

Legend: [1]: *Artemisia herba-alba* ; [2]: *Artemisia absinthium* ; [3]: *Artemisia annua*

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