



Artemisia herba alba Essential Oil: GC/MS analysis, antioxidant activities with molecular docking on S protein of SARS-CoV-2

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ABSTRACTS

This study was conceived to work on *Artemisia herba alba* essential oils (EOs) originating from Eastern Morocco. We investigated the chemical properties and determined the antiradical scavenging activity. The GC-MS technique was used to elucidate the chemical composition of the two studied regions. Jerada Eo was distinguished by the existence of 1,6-Dimethylhepta-1,3,5-triene (36.44%), Camphor (22.50%), and Thujone (7.21%). While, Taourirt EO was found to be rich in Camphor (55.31%), Eucalyptol (14.64%), and Camphene (9.95%). Moreover, the free radical scavenging ability (DPPH•), and ferric reducing power assay (FRAP) were conducted. The EOs tested are found to be weakly active and to have important antioxidant potential. The docking study was also carried out by theoretical investigation with molecular docking of four active predominating components (1,6-dimethylhepta-1,3,5-triene; Chrysanthone; Eucalyptol; Alpha-pinene) against S protein of SARS-CoV-2, and all the four ligands were found to bind to the S protein 6CS2 of SARS-CoV-2 differently and that the stable complex formed as a result of these interactions may prevent the binding of ACE2 with the spike S protein of SARS-CoV-2.

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1. INTRODUCTION

Artemisia herba alba is a plant belonging to the Asteraceae family. It is called desert or white “Wormwood” in English, “Armoise” in French, or “Shih” in Morocco (Fakchich and Elachouri, 2021). This plant grows widely in arid and semi-arid climates. Besides, this plant was found to mark the steppes and the desert of the middle east (Bertella et al., 2018), North Africa (Aziz et al., 2018), and the Northwestern Himalayas (Mighri et al., 2010). The *Artemisia herba alba* leaves are characterized by a small silvery appearance, while the flowers are grouped in clusters (Hudaib and Aburjai, 2006). The presence of components of monoterpenes and sesquiterpenes gives the plant its scents and tastes (Pirbalouti et al., 2013; Moussi et al., 2017).

Paolini et al. (2010) studied the chemical variability compositions of 16 *Artemisia herba-alba* oil samples harvested in eight East Moroccan locations using Gas Chromatography (GC) and Gas Chromatography – Mass Spectroscopy (GC/MS). Detailed analysis of the essential oils led to the identification of 52 components amounting to 80.5–98.6 % of the total oil. According to their major components (camphor, chrysanthenone, and α - and β -thujone), three main groups of essential oils were found. This study also found regional specificity of the major components (Paolini et al., 2010). The richness of chemical composition of *Artemisia herba alba* received also several applications as a corrosion inhibitor of metals in aggressive media (Bouyanzer et al., 2004; Benabdellah et al., 2006; Bouklah et al., 2006; Ouachikh et al., 2009; Bammou et al., 2011; Bouyanzer et al., 2017).

Artemisia herba alba is a plant known for its various pharmacological properties such as an anti-inflammatory (Khelifi et al., 2013), antifungal (Sami et al., 2010), anticancer (Tilaoui et al., 2015), antibacterial (Younsi et al., 2016), anthelmintic (Ahmed et al., 2020),

antispasmodic (Amor et al., 2019), and antidiabetic (Bouyahya et al., 2021). In addition to that, this herb was used in folk medicine for many years against respiratory disorders, colds, abdominal aches, and kidney sand and stones (Abu-Irmaileh and Afifi, 2003), and for its safety, less toxicity, efficacy, and its availability (Asdadi et al., 2020). *Artemisia herba alba* EO has shown a promising antiviral effect against human pathogenic viruses such as the flu and other viral respiratory infections (Hatem and Shamran, 2020).

Saptura et al. (2022) demonstrated the value of bibliometric analysis in providing analytical data about a phenomenon. The findings of this study are beneficial for future research to find potential areas of Computational Chemistry that can be studied further, due to the discovery of less-researched areas. The Docking estimation is widely used to give more explanation of the chemical activity of several molecules issued from natural plants on COVID-19 (El Hadki et al., 2021; Razon, 2020; Saputra et al. 2022; Sharma and Kaur, 2021 & 2022). QSAR models were used to explain the relationship between anti-MERS-CoV activity and the structure of 43 peptidomimetic derivatives based on physicochemical descriptors using many statistical methods such as the principal components analysis (PCA), the multiple linear regression (MLR) Y-randomization test and the multiples non-linear regression (MNLR) (Hammoudan et al., 2022).

This study aims to elucidate the chemical composition of the two *Artemisia herba alba* EOs originating from Taourirt and Jerada, and to investigate their antioxidant potential using the free radical DPPH• and the ferric reducing power assay. The *in-silico* docking simulation was exhibited to predict computationally the fixation sites of four compounds named, (1,6-dimethylhepta-1,3,5-triene; Chrysanthone; Eucalyptol; α -pinene) for further SARS-CoV-2 drug design. This analysis is important, especially for

facing pandemic problems that create issue in many aspects from education, economic, to industry (Sukmawati & Maryanti, 2022; Fahrannisa *et al.*, 2022; Azzahra *et al.*, 2022; Huwaidi *et al.*, 2021; Maryanti, 2021; Afifah, 2021; Coyoca *et al.*, 2022; Anggraeni *et al.*, 2020; Hashim *et al.*, 2020; Phanse, 2021; Dirgantari *et al.*, 2020; Mulyanti *et al.*, 2020; Sangsawang, 2020)

2. METHOD

2.1. Plant Material

The aerial parts of the plant (leaves, stems, and flowers) of *Artemisia herba alba* that grow naturally in two regions in Eastern Morocco (Taourirt and Jerada) (Figure 1), were used in this study. The plant material was harvested in June (Figure 2).

2.2. Preparation of *Artemisia Herba Alba* Essential Oils

The EOs were extracted in two cooperatives located in Jerada and Taourirt,

two cities in Eastern Morocco (Figure 1). The plant material was dried naturally in a shady room at a temperature of 25°C for five days until total dryness.

Afterward, the EOs were extracted for about 2h using the steam distillation method which consists first of boiling water in a boiler to obtain steam, this steam is sent into the still (in stainless steel) which previously contains the plant material to be distilled, crossing the plant the steam will burst the aromatic bags of the plant which contain the essences.

The vapor charged with essences will pass through a cooling system (Condenser) to become liquid again which will be collected in the Essencier, and at this level that the EO separates from the Hydrolates which will be recovered and returned to the boiler for a new cycle. Finally, the EO obtained was stored at 4°C in tight vials for further use.

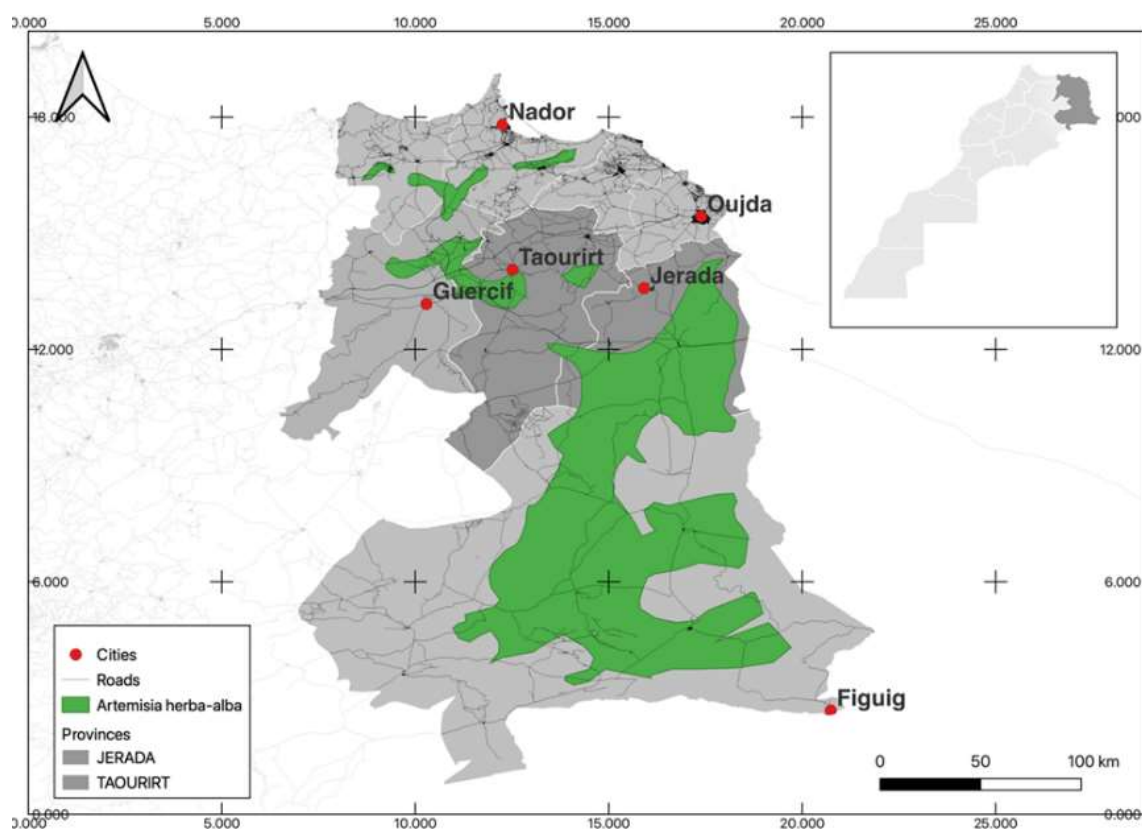


Figure 1. Geographical distribution of *Artemisia herba alba* in Eastern Morocco.



Figure 2. A. herba alba of Jerada, Eastern Morocco.

2.3. Qualitative and Semi-quantitative Analysis of *Artemisia Herba Alba* using GC-MS

The obtained EOs were analyzed using gas chromatography (Shimadzu GC-2010) coupled with the Mass spectroscopy GC-MS-QP2010) according to the protocol described by [Dalli et al. \(2021\)](#). Helium inert gas was used as a carrier its pressure was adjusted to a pressure of 100 KPa. Further modifications were realized such as the oven temperature that was maintained at 50°C for about 1 min, then a gradient of about 10°C/min was followed to reach an oven temperature of 150°C.

Afterward, a gradient of 20°C/min was set to reach a temperature of 250°C. Concerning the analysis of the samples, a quantity (1 µL) was taken from each EOs and diluted in hexane. After all the samples were prepared an injection using split mode with a ratio of (25:1). For the identification of the different constituents a comparison of the retention time of each compound with its MS data using the National Institute of Standards and Technology (NIST) computer library. Detailed information for the use of GC-MS is reported in elsewhere.

2.4. Antioxidant Potential of *Artemisia Herba Alba* Essential Oils

To demonstrate the antioxidant potential of the extracted *Artemisia herba alba* EOs,

the free radical scavenging activity against the DPPH• and the ferric reducing power assay (FRAP) were used.

2.4.1. Free radical scavenging ability against DPPH•

The DPPH assay is the most frequently used assay and the simplest method that offers the first approach for evaluating antioxidant activity ([Zhong and Shahidi, 2015](#)). This method aims to evaluate the antioxidant potential of the different extracts of *Artemisia herba alba* EO. From each EO different concentrations were prepared (50, 100, 200, 400, and 600 mg/mL). 200 µl was taken from each concentration and mixed with 1.8 ml of DPPH (0.5mM). The reaction mixture was then incubated in dark conditions for 20 min at room temperature. The absorbance was measured at 517 nm against the blank ([Dalli et al., 2021](#)). All measurements were performed in triplicate. The inhibition percentage was calculated according to the Eq. (1) ([Elshafie et al., 2020](#)):

$$\% \text{ Radical scavenging activity} = \frac{(Abs_{Control} - Abs_{sample})}{Abs_{Control}} \times 100 \quad (1)$$

2.4.2. Ferric reducing power assay (FRAP)

The ferric reducing antioxidant power (FRAP) assay aims to evaluate the antioxidant potential of the EOs by measuring the increase of absorbance in the reaction mixtures ([Alam et al., 2016](#)). For this reason,

different concentrations were prepared and then a quantity of 0.5 ml of each concentration was taken and mixed with 1.25 ml of phosphate buffer (0.2M, pH 6.6) and 1.25 ml of potassium ferricyanide $K_3Fe(CN)_6$ (1%w/v). This method is mainly based on the reduction of Fe^{3+} found in $K_3Fe(CN)_6$ to Fe^{2+} . then, the reaction mixture was incubated at 50°C for 20 min in a water bath. After cooling the reaction was stopped by adding 1.25 mL of Trichloroacetic acid (10% w/v). The mixture was centrifuged at 3000 rpm for 10 minutes. An aliquot of 1.25 ml was taken from the supernatant and mixed with 1.25 ml of distilled water and 0.25 ml of ferric chloride (0.1% w/v). The absorbance was measured at 700 nm against a blank. Ascorbic acid was used as a positive control. All measures were performed in triplicate (Azizi *et al.*, 2021).

2.5. Molecular Docking Study

SARS-CoV2 are mainly classified into four categories viz. α -CoV, β -CoV, γ -CoV, and δ -CoV, of which the latest, classified as SARS-CoV-2, belongs to the β -CoV category. It has four different proteins such as spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Figure 3). Recent studies showed that β -Coronaviruses enter human host cells via the angiotensin 2 converting enzyme receptors (ACE2) in humans, causing severe acute respiratory inflammation (Hattori *et al.*, 2021). The spike protein on the surface of SARS-CoV-2 is a major antigen and its adhesion to the human ACE2 receptor plays an essential role in viral entry into host cells (Jungreis *et al.*, 2021; Touzani *et al.*, 2020).

Four active molecules (1,6-dimethylhepta-1,3,5-triene-; chrysanthone; eucalyptol; alpha-pinene) presenting in *Artemisia herba*

alba essential oil were studied computationally (*in silico*) by evaluating their toxicity, their physicochemical parameters calculated to ensure their suitability with Lipinski's rules. Also, their antiviral activity was assessed by studying their interactions with SARS-CoV-2 Protein S using MOE program (Figure 4).

2.5.1. Preparation of the protein structure

The receptor-binding domain (RBD) of protein S of SARS-CoV-2 has been uploaded to the PDB data bank under the code: 7KGJ. The protein is formed by two chains A and B, of which A is the RBD domain of glycoprotein S and B is a synthetic nanobody assembly. The structure was prepared by the Molecular Operating Environment (MOE 2015.10) by removing water, heteroatoms, and the B chain. The A chain was then protonated, its active site determined, and its potential energy fixed to avoid any potential change during docking (Figure 5).

2.5.2. Preparation of the ligands

The four ligands were drawn by the ChemDraw 20.1.1 program and then converted into a 3D format. Their energy is then minimized using the dynamic MM2 method and saved in PDB format.

2.5.3. Docking protocol

The calculations of the Docking and the 2D/3D protein-ligand interactions were performed with the MOE program using the triangle matcher method under rigid Docking.

2.6. Statistical Analysis

The statistical tests were applied using GraphPad Prism, version 6.00 (GraphPad Software, San Diego, CA, USA).

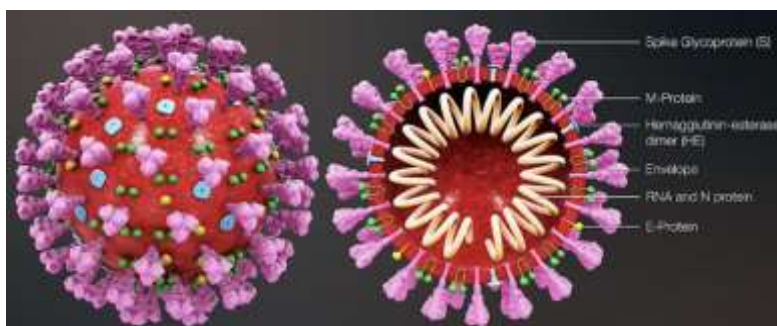


Figure 3. The 3D Coronavirus Structure (Touzani et al., 2020).

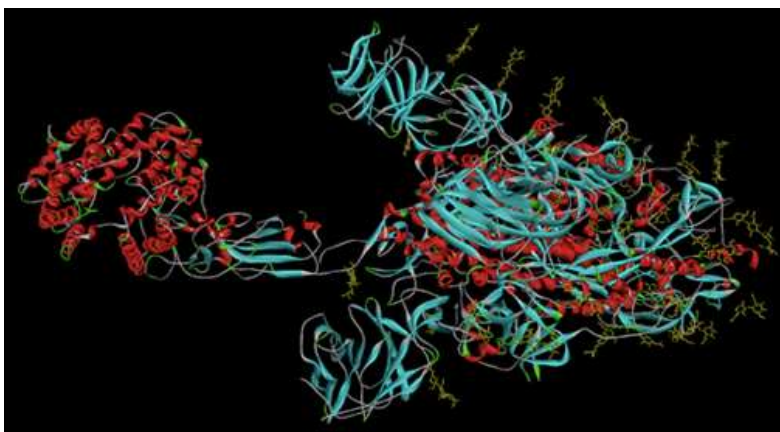


Figure 4. Crystal structure of S protein 6CS2 bound to ACE2.

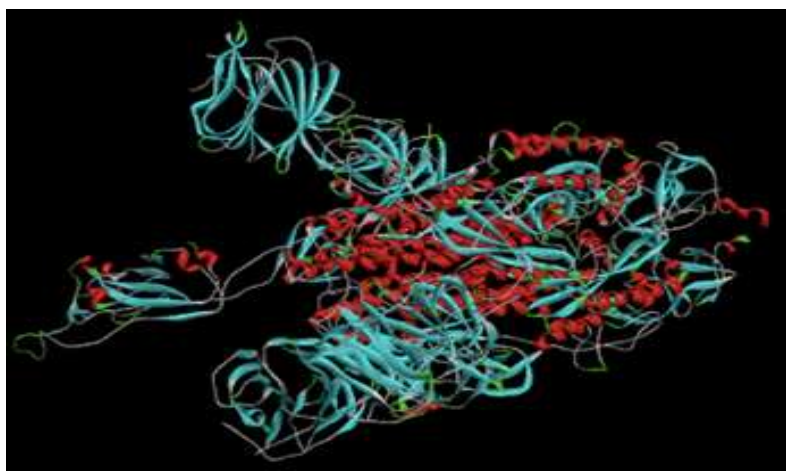


Figure 5. Prepared S protein 6CS2.

3. RESULTS AND DISCUSSION

3.1. Chemical Composition

Analysis of the *Artemisia herba alba* EOs originating from Jerada and Taourirt permitted the identification of 26 and 23 constituents respectively. The results drafted in **Table 1** and **Figure 6** represent respectively the total ion chromatogram and chemical components identified in the EOs using GC-MS. The data show that the major

compounds in Jerada EO are found to be 1,6-Dimethylhepta-1,3,5-triene (36.44%), Camphor (22.50%), Thujone (7.21%), Eucalyptol (5.96%), Camphene (4.08%), while Taourirt EO was predominated by Camphor (55.31%), followed by Eucalyptol (14.64%), then Camphene (9.95%), 3-Thujanone (3.07%), and, 3,3,6-Trimethyl-1,4-heptadien-6-ol (2.33%) (**Figure 7**).

These main five constituents comprised more than 76.19% of the total composition of

Jerada EO and 85.30% of Taourirt EO, and all of the remaining individual constituents in Jerada comprised 23.80% of the concentration, with a total of 99.99% of the volatiles identified, and in Taourirt the individual constituents comprised 14.08% of the concentration, with a total of 99.38% of all constituents. A review by [Mohamed et al.](#)

(2010) indicated that *Artemisia herba alba* Eo was extensively investigated, and is characterized by the existence of monoterpenoids, mainly oxygenated ones, such as 1,8-cineole, chrysanthenone, chrysanthenol, α/β -thujones, and camphor as the major components.

Table 1. Chemical constituents identified in *Artemisia herba alba* essential oils from two regions.

N	Nom	Tr (min)	% Jerada	% Taourirt
1	Santolina triene	4.558	-	0.49
2	Tricyclene	4.800	0.38	0.69
3	Alpha-Pinene	4.975	1.07	0.43
4	Camphene	5.217	4.08	9.95
5	Cis-Pinen-3-ol	5.292	0.16	-
6	Thujene	5.583	0.53	-
7	Beta-Pinene	5.650	0.37	0.34
8	3,3,6-Trimethyl-1,4-heptadien-6-ol	5.950	-	2.33
9	1,2,4-Trimethylbenzene	5.900	0.13	-
10	(+) -4-Carene	6.250	0.20	-
11	1-Isopropyl-2-methylbenzene	6.375	0.70	-
12	Benzene, 2-ethyl-1,3-dimethyl	6.400	-	1.02
13	D-Limonene	6.442	2.38	0.92
14	Eucalyptol	6.500	5.96	14.64
15	Cyclopentene, 3-isopropenyl-5,5-dimethyl	6.908	0.38	-
16	Ocimene	6.933	-	0.42
17	Cis-3-Hexenyl iso-butyrate	7.092	-	0.41
18	1,5-Heptadien-4-ol, 3,3,6-trimethyl	7.292	-	1.90
19	3,3-Dimethyl-6-methylenecyclohexene	7.625	2.37	-
20	Chrysanthone	7.667	1.24	3.07
21	Thujone	7.833	7.21	0.46
22	1,6-Dimethylhepta-1,3,5-triene	7.975	36.44	-
23	Trans-Pinocarveol	8.233	-	1.03
24	Camphor	8.300	22.50	55.31
25	P-Mentha-1(7),8(10)-dien-9-ol	8.450	-	1.74
26	Santolina epoxide	8.592	-	1.13
27	Borneol	8.608	1.00	0.98
28	4-Carvomenthenol	8.767	0.62	0.61
29	(1R)-(-)-Myrtenal	9.100	-	0.77
30	2-Isopropylidene-5-methylcyclohexanone	9.683	0.42	-
31	Bicyclo[3.1.1]hept-2-en-4-ol, 2,6,6-trimethyl-, acetate	9.950	1.56	-
32	Trans-alpha-Bergamotene	10.083	-	0.30
33	Bornyl acetate	10.350	-	0.44
34	1,3-Cyclopentadiene, 5,5-dimethyl-2-ethyl	10.842	0.41	-
35	(1,3-Dimethyl-2-methylene-cyclopentyl)-methanol	11.000	6.50	-
36	3,5-Heptadienal, 2-ethylidene-6-methyl-	11.775	3.38	-
Total identified			99.99	99.38

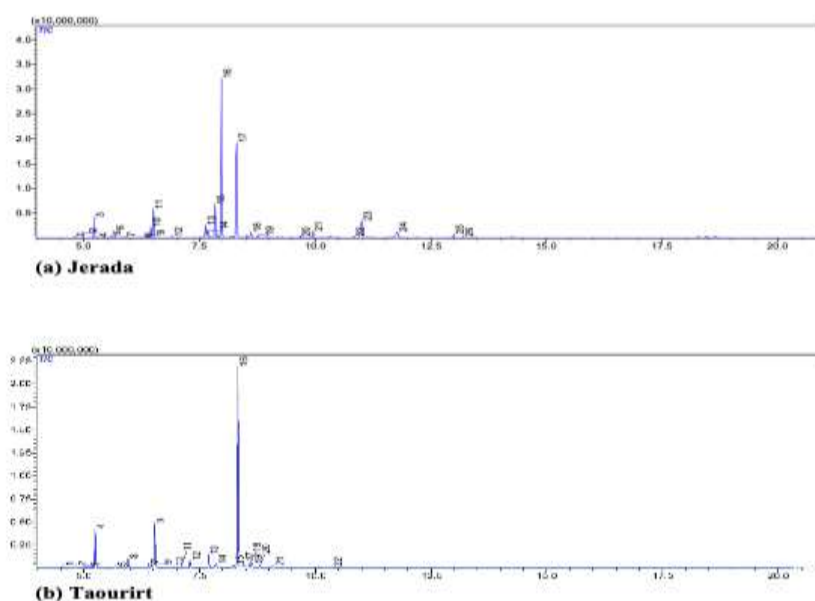


Figure 6. Total ion chromatogram of *Artemisia herba alba* EOs of (a) Taourirt and (b) Jerada.

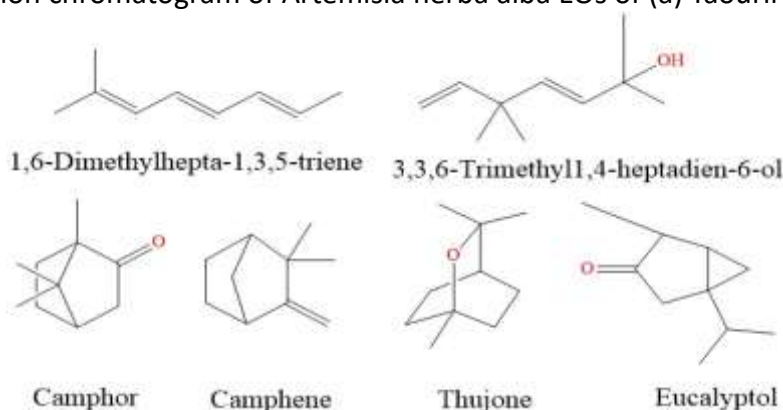


Figure 7. Main identified chemical compounds.

According to Mighri et al. it was reported the existence of some EOs that are dominated by major compounds such as (camphor, α or β -thujone, chrysanthenone, chrysanthenyl acetate, or davanone), and other EOs that are distinguished with the presence of two or more of these compounds at appreciable levels. Ed-Dra, and Filali (Ed-Dra et al., 2021) have reported that the most abundant compounds of the *A. herba alba* EO from the East of Morocco (Talsint) were Davanone ($38.25\% \pm 1.25\%$), Davana Ether Isomer 1 and 2 ($9.91 \pm 0.47\%$ and $8.25 \pm 0.25\%$, respectively), 1,2 Dehydro-3-hydroxyisodavanone ($6.33 \pm 0.67\%$) and Camphor ($6.31 \pm 0.16\%$).

Davanone was identified for the first time as the major component of *Artemisia herba alba* EO, harvested from Morocco. β -thujone

(24.34%), camphor (22.23%), α -thujone (14.56%), and 1,8-cineole (10.3%) were also observed as well as main components in *Artemisia herba alba* from Agadir region (Moussii et al., 2020). A study performed by Sami et al. (2010) on the aerial parts of Tunisian *Artemisia herba alba* has shown the existence of a multitude of chemical compounds among them we cite the presence of Oxygenated monoterpenoids with an amount of 78.6%, such as camphor (39.1%), chrysanthenone (15%) and cis-thujone (7.8%). While the total oxygenated sesquiterpenes amount was 13.9% (9.5% (E)-patchenol, 3.1% (Z)-patchenol, 0.8% spathulenol and 0.5% ar-turmerone).

In another study conducted on *Artemisia herba alba* originating from south Jordan, it was demonstrated a great richness with

Oxygen-containing monoterpenes mainly 1,8-cineole (20.1%), β -thujone (25.1%), α -thujone (22.9%), and camphor (10.5%) (Abu-Darwish *et al.*, 2015). While in the EO of Bechar, Southwestern Algeria is was noted to be constituted by 80.3% of oxygenated monoterpenes, followed by 10.8% of monoterpene hydrocarbons (10.8%), and a very low quantity of oxygenated sesquiterpenes (0.2 %). Of all the identified compounds, α -thujone (48.0%), β -thujone (13.4%), and camphor (13.1%) were the main major compounds, while other components found in a small amount are camphene (3.6%), γ -terpinene (1.4%), borneol (1.3%), and p-cymene (1.0%) (Ouguirti *et al.*, 2021).

The difference between the two studied sites could mainly be attributed to the different climatic and edaphic conditions (Dalli *et al.*, 2021). For example, the climate of Jerada is arid, while Taourirt's climate is considered semi-arid. This stress caused by the lack of water could play a crucial role in the EO accumulation via a higher density of oil glands due to the reduction in leaf area. These different mentioned effects could be helpful for the plant to assure better growth, which leads to high EOs accumulation in the aerial parts. Following a bibliographic study, our results are comparable to certain research results, but different compared to others. The variability in EO chemical composition from plants grown in different geographical locations has led to many EOs dependent chemotypes assigned to the plant which suggests differences in the volatile composition of the plant material that could be attributed to several factors such as the geographic origin of the plant and chemotype.

3.2. Antioxidant Activities

The antioxidant activity was performed using an antiradical scavenging activity assay against the DPPH• and the ferric reducing power assay (FRAP). The results obtained

indicated that the antioxidant activity increases with the increase of the EOs concentrations. The recorded IC₅₀ of *Artemisia herba alba* EOs from Jerada and Taourirt are respectively, 115.08 ± 2.58 mg/ml and 380.27 ± 30.28 mg/ml. While the ascorbic acid used as control gave an IC₅₀ of 0.029 ± 0.49 mg/ml ($p < 0.001$) (Table 2). However, based on previous studies, the efficiency of phenolic compounds as anti-radicals and antioxidants depends on many factors. One main factor is the number of hydroxyl groups directly bonded to the aromatic rings (Sroka and Cisowski, 2003; Mohammed *et al.*, 2021). Another antioxidant activity test used in this study was the ferric reducing antioxidant power (FRAP) assay. The results showed also that the antioxidant activity increases with the increase of the EOs concentrations. The IC₅₀ value of the Os of Jerada and Taourirt are respectively, 13.39 ± 0.058 mg/ml ($p > 0.05$) and 161.75 ± 16.20 mg/ml ($p < 0.001$). The ascorbic acid used as positive control has an IC₅₀ of 0.87 ± 0.058 mg/ml (Table 3). As shown in Table 2, *Artemisia herba alba* EO of Jerada exhibited a high antioxidant ability against DPPH• compared to *Artemisia herba alba* EO of Taourirt. The results tabulated in Table 3 indicated that the *Artemisia herba alba* EO originating from Jerada had the strongest ferric reducing power, while the EO originating from Taourirt exhibited relatively weak ferric reducing antioxidant effects compared with that of Jerada region and with the ascorbic acid used as control. A study from Algeria showed that the EO of *Artemisia herba alba* exhibited a distinct antioxidant activity (Amina *et al.*, 2022). Indeed, in another research exhibited by (Kadri and Goubi, 2022), it was mentioned that *Artemisia herba alba* EO had similar free radical scavenging activity compared to standard ascorbic acid which means a higher antioxidant potential in comparing to our findings.

Table 2. The IC₅₀ of the different extracts for DPPH and FRAP methods.

	Jerada EO	Taourirt EO	Ascorbic acid
IC ₅₀ (mg/ml) DPPH	115.082 ± 2.58****	380.27 ± 30.28****	0.74 ± 0.029
IC ₅₀ (mg/ml) FRAP	13.39 ± 0.058 ^{ns}	161.75 ± 16.2****	0.87 ± 0.05

Table 3. Toxicity risk of *Artemisia herba alba* molecules calculated by Osiris.

RISK OF TOXICITY					
COMPOUNDS	MW(g/mol)	MUT	TUM	IRRI	REP
a	136.238	+++	+++	+++	+++
b	122.237	+++	+++	+++	+++
c	276.28	+++	+++	+++	+++
d	154.25	+++	+++	+	+++

The difference in the chemical composition of each EO may be strongly related to the antioxidant effect noted. The statistical analysis showed a highly significant difference between the studied EOs and the ascorbic acid used as a control for the DPPH and the FRAP assays, which made it clear that these EOs are less effective than the synthetic ones. These obtained results were in accordance with those obtained by Lopes-Lutz *et al.*, (2008) which indicated that the EOs predominated by non-phenolic compounds have shown a low antioxidant activity in some *Artemisia* species.

3.3. Molecular Docking Study

3.3.1. Risk of toxicity

During the research phase of drug candidates, their toxicity is one of the most important and feared parameters for developers (Marchant, Briggs, and Long, 2008). Therefore, it is essential for us to predict the toxicity of our four molecules (1,6-dimethylhepta-1,3,5-triene [a] ; Chrysanthone [b] (**Figure 8**); Eucalyptol [c]; α -pinene [d] (**Table 3**), before any other study attempt. The results presented in (**Table 4**) show that only α -pinene could present a slight irritation risk. Below are the data reported by the Osiris toxicity risk study.

3.3.2. Lipinski's rule

Several methods, most of them based on physicochemical parameters, have been

proposed to study the similarity to a drug. Lipinski's rule is based on the search for properties common to 2245 molecules extracted from the WDI (World Drug Index) which have at least reached phase II of clinical trials and therefore present a priori good values of solubility and intestinal permeability (Lipinski *et al.*, 1996). The "Lipinski rule" thus proposes threshold values for molecular weight (PM<500), the number of hydrogen bond acceptors and donors (ALH< 10 and DLH< 5), the number of rotational bonds (N-rot< 10), and the water/octanol partition coefficient (logP<5). According to this rule, a compound is more susceptible to poor oral bioavailability when it has more than one violation of this rule. The Lipinski criteria (**Table 5**) for all four molecules show no violations.

3.3.3. Post Docking Results

The results of molecular docking of the four molecules (a, b, c, d) with the receptor-binding domain (RBD) of SARS-CoV-2 protein S encoded 7kgj have been reported (**Figure 9**). The 2D/3D interactions of the complex formed by the four ligands are shown in **Figures 10,11, and 12**. Among the four drug-candidate molecules, Chrysanthone has the lowest binding energy (S= -4.90; E= 8.298kJ/mol) (**Figure 10**), followed by Eucalyptol (S=-4.370; E= -5.772 kJ/mol) (**Figure 10**) then comes 1,6-dimethylhepta-1,3,5-triene (S= 3.751; E= -6.045 kJ/mol)

(Figure 8) finally alpha-pinene ($S=-3.551$; $E=-5.699$ kJ/mol) (Figure 12). Based on the S-score (Figure 9) which considers all the docking parameters, we see that

Chrysanthone ($S=-4.90$) is the most binding conformation of chrysanthone and therefore the most likely to form a more stable and anchored complex with Protein 7kgj.

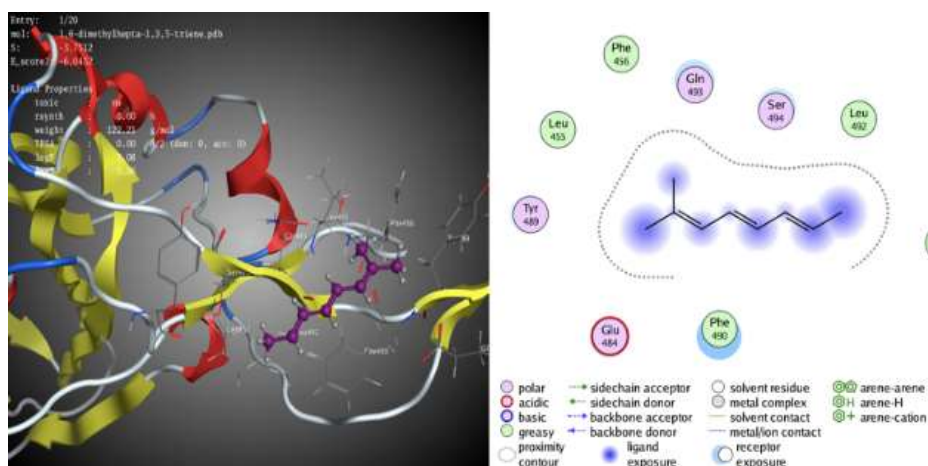


Figure 8. 2D/3D interaction of 1,6-dimethylhepta-1,3,5-triene with 7kgj protein.

Table 4. Osiris analysis of compounds 1–4.

Compound	Toxicity Risks	Solubility	Drug-Score
 a	Toxicity Risks	cLogP [?]	TPSA [?]
	mutagenic	3.55	0.0
	tumorigenic	Solubility [?]	Druglikeness [?]
	irritant	-2.04	-3.89
 b	reproductive effective	Molweight	Drug-Score [?]
	122.0	0.45	
	Toxicity Risks	cLogP [?]	TPSA [?]
	mutagenic	0.89	75.99
 c	tumorigenic	Solubility [?]	Druglikeness [?]
	irritant	-2.98	-1.3
	reproductive effective	Molweight	Drug-Score [?]
	276.0	0.55	
 c	Toxicity Risks	cLogP [?]	TPSA [?]
	mutagenic	2.14	9.23
	tumorigenic	Solubility [?]	Druglikeness [?]
	irritant	-2.55	-3.64
 c	reproductive effective	Molweight	Drug-Score [?]
	154.0	0.48	

Table 5. Lipinski's rule as assessed by the MOE

Compound	MW(g/mol)	Lipinski Rule				
		Log P	NHBA	NHBD	N-rotB	LR-app
a	136.238	4.056	0	0	2	None
b	122.237	1.525	5	2	1	None
c	276.28	2.948	1	0	0	None
d	154.25	3.994	0	0	0	None

MW: molecular weight, NHBA: number hydrogen bond acceptor, NHBD: number hydrogen bond donors, N-rotB: number rotative bond, LR-app: Lipinski rule appreciation.

This is due to the formation of intramolecular hydrogen bonds between the carbonyl groups -CO and -OH, acceptor Oxygen bonds with Arg346, tyr351 but also π - π bonds between the arena and Asn450 (**Figure 10**). Lightly toxic: (+), Not toxic (+++). MW: molecular weight, MUT: Mutagenic, TUM: Tumorigenic, IRRI: Irritant, RE: Reproductive effective. The post-docking results performed by MOE showed strong interactions towards the four molecules,

which confirms the previous evaluation shown by Osiris, especially Chrysanthone (b) which showed the formation of oxygen acceptor bonds with Arg346, tyr351, π - π bonds of arena-H and Asn450 but also the formation of intramolecular hydrogen bonds. Thus, it can be concluded that Chrysanthone can form an anchored and stable complex with the receptor-binding domain (RBD) of SARS-CoV-2 Protein S.

	mol	mseq	S	E_score1	rmsd_refine	E_conf	E_place	E_refine	E_score2
1	chrysanthone.pd	3	-4.4387	-9.1735	1.7626	6.6306	-50.1907	-23.3112	-4.4387
2	chrysanthone.pd	3	-4.5588	-9.1307	1.1770	2.1385	-43.7115	-19.6595	-4.5588
3	chrysanthone.pd	3	-4.2826	-8.8132	1.5885	7.1028	-51.9256	-16.0889	-4.2826
4	chrysanthone.pd	3	-4.5676	-8.6350	1.7393	4.2156	-46.7588	-20.7698	-4.5676
5	chrysanthone.pd	3	-4.9003	-8.2988	1.2945	4.3345	-52.5851	-21.8643	-4.9003
6	eucalyptol.pdb	4	-3.5601	-6.5303	1.9017	-29.7939	-20.2879	-10.4645	-3.5601
7	eucalyptol.pdb	4	-3.7759	-6.1923	0.9996	-29.9329	-22.8687	-11.4965	-3.7759
8	eucalyptol.pdb	4	-3.9821	-6.0697	2.5920	-29.8785	-17.5939	-11.0595	-3.9821
9	1,6-dimethylhep	1	-3.7512	-6.0452	1.1850	0.3802	-18.4733	-11.9215	-3.7512
10	eucalyptol.pdb	4	-3.8850	-5.9244	1.2164	-29.8849	-17.6657	-12.6296	-3.8850
11	eucalyptol.pdb	4	-4.3701	-5.7728	1.9072	-29.7899	-13.7104	-18.5375	-4.3701
12	alpha-pinène.pd	2	-3.5513	-5.6994	1.4333	31.4813	-22.1687	-9.7797	-3.5513
13	1,6-dimethylhep	1	-3.6054	-5.6914	0.9254	0.5191	-34.2878	-9.6617	-3.6054
14	alpha-pinène.pd	2	-3.3830	-5.6687	0.7402	31.5160	-21.4812	-9.8651	-3.3830
15	1,6-dimethylhep	1	-3.6288	-5.6510	1.1326	0.1937	-36.4157	-11.4379	-3.6288
16	alpha-pinène.pd	2	-3.5629	-5.5842	2.5261	31.4799	-21.5649	-10.0850	-3.5629
17	alpha-pinène.pd	2	-3.4906	-5.5544	1.5829	31.5703	-30.2214	-10.5664	-3.4906
18	alpha-pinène.pd	2	-3.3822	-5.5034	1.3602	31.4294	-32.3366	-9.6106	-3.3822
19	1,6-dimethylhep	1	-3.6707	-5.4348	1.3326	0.2079	-19.4715	-11.0659	-3.6707
20	1,6-dimethylhep	1	-3.5627	-5.2621	1.0112	0.1769	-24.8853	-10.5271	-3.5627

Figure 9. Docking result of the four molecules with the SARS-CoV-2 protein S receptor binding domain.

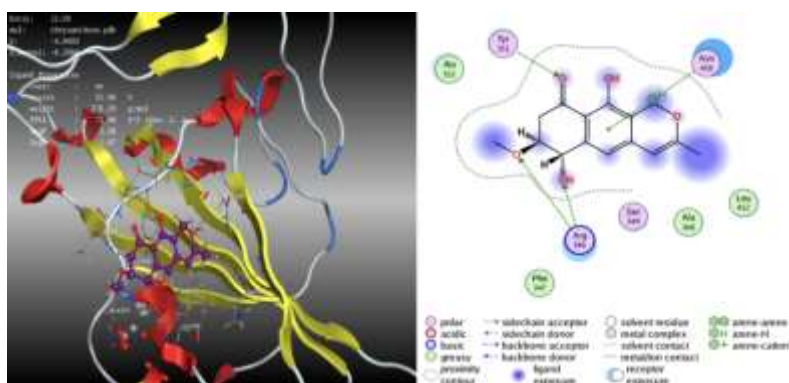


Figure 10. 2D/3D interaction of Eucalyptol with the 7kgj protein.

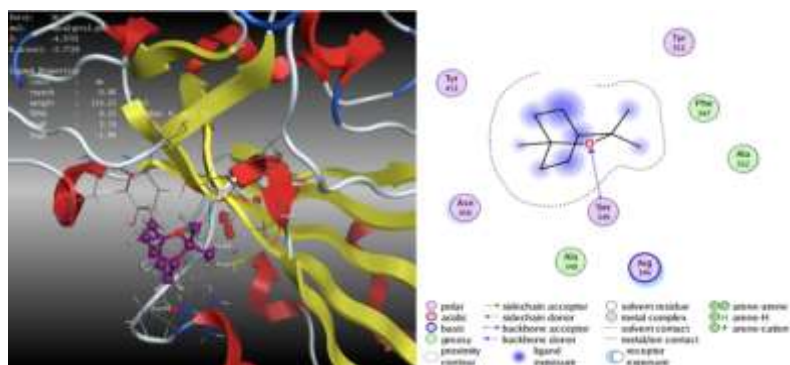


Figure 11. 2D/3D interaction of Chrysanthone with the 7kgj protein.

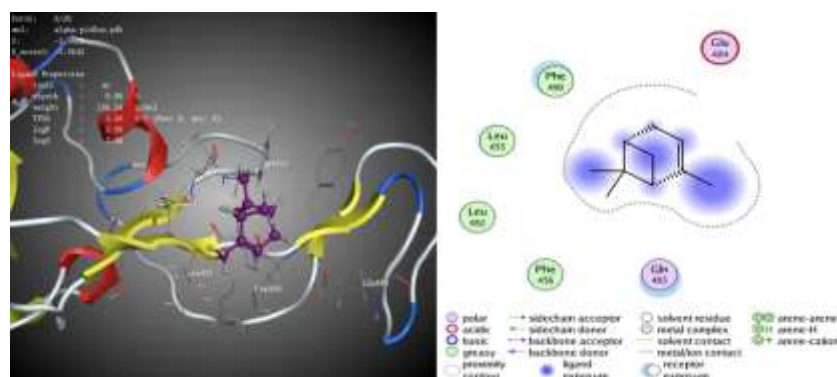


Figure 12. 2D/3D interactions of alpha-pinene with the 7kgj protein.

4. CONCLUSION

The present work showed that *Artemisia herba alba* EO of Jerada was marked by codominance of three main components such 1,6-Dimethylhepta-1,3,5-triene, Camphor, and Thujone, which are not described in the literature, and seems characteristic of Eastern Morocco. While Taourirt EO was found to be rich with Camphor, Eucalyptol, and Camphene. The obtained results demonstrated that the Jerada EOs possesses a low antioxidant activity compared to Vitamin C, and it was found to be more active compared to the EO of Taourirt. The four molecules have been evaluated computationally for toxicity by Osiris test, none of them showed toxic effects except α -pinene which presents a very low

risk of irritation. Their similarity to a drug is estimated for 1,6-dimethylhepta-1,3,5-triene (a) at 54%; Chrysanthone (b) 55%; Eucalyptol(c) 48% and alpha-pinene 31%. All molecules showed high respect for Lipinski's rule. Our findings suggest that chrysanthone could play a potential role in preventing further binding of the virus to ACE2 which is the gateway of SARS-CoV-2 into the human body. Indeed, further *in vitro* and then *in vivo* studies are needed to confirm the obtained results.

5. AUTHORS' NOTE

The authors declare that there is no conflict of interest regarding the publication of this article. The authors confirmed that the paper was free of plagiarism.

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