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Original Article

Molecular docking study of the main phytochemicals of some medicinal plants used against COVID-19 by the rural population of Al-Haouz region, Morocco

[Estudio de acoplamiento molecular de los principales fitoquímicos de algunas plantas medicinales utilizadas contra el COVID-19 por la población rural de la región de Al-Haouz, Marruecos]

Ridwane Ghanimi[1]*, Ahmed Ouhammou[2], Yassine El Atki[3], Mohamed Cherkaoui[1]

[1]Laboratory of Pharmacology, Neurobiology, Anthropobiology, Environment and Behaviour, Department of Biology, Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakech, BP 2390, 40000, Morocco.
[2]Laboratory of Microbial Biotechnologies, Agrosciences and Environment (BioMAgE), Agrosciences, Phytobiodiversity and Environment Team, Regional Herbarium 'MARK', Department of Biology, Faculty of Sciences Semlalia , Cadi Ayyad University, PO. Box 2390, Marrakech, 400001, Morocco.
[3]Laboratory of Physiology Pharmacology and Environmental Health, Department of Biology, Faculty of Sciences Dhar Mehraz,Sidi Mohamed Ben Abdellah University, Fez, Morocco.
*E-mail: ghanimiridwane@gmail.com, ridwane.ghanimi@ced.uca.ma

Abstract

Context: The infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a global health emergency. The management of this crisis requires the discovery of new drugs able to cure or reduce the severity of SARS-CoV-2.

Aims: To explore the medicinal plants consumed by the rural population of Al-Haouz region against the emergence of the COVID-19, and to assess *in silico* the main phytochemicals present in the essential oils and the extracts of these medicinal plants, as potential inhibitors of the COVID-19 main protease (M^{pro}).

Methods: The survey was conducted through a semi-structured questionnaire among 85 respondents aged 30 years and above, in the Al-haouz region, Morocco. AutoDock Vina, was used to assess the binding affinity of the phytochemicals to the M^{pro}.

Results: Eleven wild medicinal species were cited; 10 belonging to the *Lamiaceae* family and one to the *Compositae* family. *Thymus saturejoides* Coss., *Artemisia herba-alba* Asso.and *Mentha suaveolens* Ehrh. were respectively the three most cited species during the survey. The rosmarinic acid (-7.7 kcal/mol), hesperetin (-7.2 kcal/mol), gallocatechin (-7.2 kcal/mol) and cyasterone (-7.2 kcal/mol) have shown the higher inhibitory potential against covid-19 M^{pro} respectively.

Conclusions: In addition to their different recognized biological activities, the medicinal plants used in the Al-Haouz region have shown good inhibitory potential against SARAS-CoV-2 M^{pro}. Furthermore, the phytochemicals that exhibited the highest inhibitory potentials in this virtual study require further investigation *in vitro* and *in vivo*.

Keywords: COVID-19; ethnomedicine; medicinal plants; molecular docking; Morocco; SARS-CoV-2.

Resumen

Contexto: La infección por el coronavirus 2 del síndrome respiratorio agudo severo (SARS-CoV-2) es una emergencia sanitaria mundial. El manejo de esta crisis requiere el descubrimiento de nuevos medicamentos capaces de curar o reducir la gravedad del SARS-CoV-2.

Objetivos: Explorar las plantas medicinales consumidas por la población rural de la región de Al-Haouz frente a la aparición del COVID-19, y evaluar in silico los principales fitoquímicos presentes en los aceites esenciales y los extractos de estas plantas medicinales, como potenciales inhibidores. de la proteasa principal COVID-19 (M^{pro}).

Métodos: La encuesta se realizó a través de un cuestionario semiestructurado entre 85 encuestados de 30 años o más, en la región de Al-haouz, Marruecos. Se utilizó AutoDock Vina para evaluar la afinidad de unión de los fitoquímicos al M^{pro}.

Resultados: Se citaron once especies medicinales silvestres; 10 pertenecientes a la familia *Lamiaceae* y una a la familia *Compositae*. *Thymus saturejoides* Coss., *Artemisia herba-alba* Asso. y *Mentha suaveolens* Ehrh. fueron, respectivamente, las tres especies más citadas durante la encuesta. El ácido rosmarínico (-7,7 kcal/mol), la hesperetina (-7,2 kcal/mol), la galocatequina (-7,2 kcal/mol) y la ciasterona (-7,2 kcal/mol) han mostrado el mayor potencial inhibitorio frente al covid-19 M^{pro}, respectivamente.

Conclusiones: Además de sus diferentes actividades biológicas reconocidas, las plantas medicinales utilizadas en la región de Al-Haouz han mostrado un buen potencial inhibitorio contra SARAS-CoV-2 M^{pro}. Además, los fitoquímicos que exhibieron los potenciales inhibidores más altos en este estudio virtual requieren más investigación *in vitro* e *in vivo*.

Palabras Clave: acoplamiento molecular; COVID-19; etnomedicina; Marruecos; plantas medicinales; SARS-CoV-2.

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INTRODUCTION

The infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was initiated from the Wuhan city of China in December 2019, and within a couple of months, it has turned out to be a global health emergency (Chakraborty and Maity, 2020). As of September 3, 2021, there are more than 218 946 836 confirmed cases of COVID-19 worldwide, including 4 539 723 deaths reported by WHO (WHO, 2021).

In Morocco, the situation is very sensitive because of the high number of contaminated cases. On 3 September 2021, the Bulletin of Moroccan Public Health related to COVID-19 revealed 876 732 confirmed cases, including 12 923 deaths (Moroccan Health Ministry, 2021). This situation requires all possible interventions to reduce the spread of this virus (El Kahkahi et al., 2020).

The current pandemic constitutes a serious public health emergency, particularly deadly for vulnerable populations and communities, due to health care providers who are not sufficiently prepared to manage the infection (Pfefferbaum and North, 2020). However, the Al-Haouz region, which accommodates several vulnerable communities, has shown a low number of cases compared to other Moroccan regions, which have shown a very high number of infections despite their access to personal hygiene equipment (Moroccan Health Ministry, 2021).

The reasons for the low contamination rate in Al-Haouz communities could be due to their diets. One of the dietary characteristics of the Al-Haouz population is the consumption of some aromatic and medicinal plants (MAP) in their daily meals. Moreover, MAP contain several bioactive molecules that could inhibit SARS-CoV-2, hence the interest to study *in silico*, *in vitro* and *in vivo* the capacity of these phytochemicals against SARS-CoV-2.

The first objective of this study was to explore the medicinal plants used against COVID-19 by the local population of Al-Haouz region. The second objective was to assess *in silico* the main phytochemicals present in the essential oils and the extracts of the cited plants as potential inhibitors of the COVID-19 main protease (M^{pro}), which is one of the famous viral targets for the discovery of antiviral molecules against SARS-CoV-2.

MATERIAL AND METHODS

Study area

The study area was the Al-Haouz region (Fig. 1), situated in the central part of Morocco, and occupies approximately 20 500 km^2 covering the area between latitudes 31° and 32°30′ N and longitudes 7° and 10° W (Elidrissi et al., 2020).

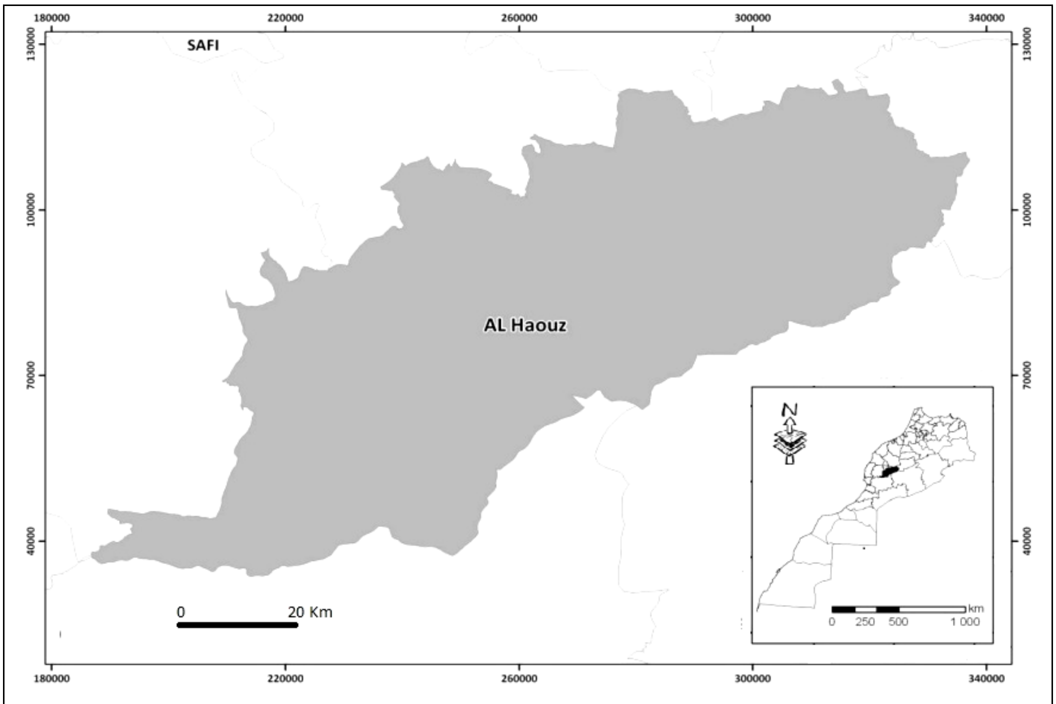


Figure 1. The geographical location of the Al-Haouz region.

Data collection

This ethnobotanical study was carried out between September and December 2020 on the Al-Haouz region (6212 km^2), located in the western slope of the Central High Atlas Mountains (Ramaoui et al., 2008). The Messiwa people are the original population of this region, which is dominated by rural communities (88%) with an economy mainly based on agriculture and tourism (HCP, 2014). The survey was conducted among the Messiwa population through college students who acted as a link with their parents due to the sanitary precautions and confinement. Informed consent was obtained from the population before starting the survey. Eligibility was to be of legal age, able to answer our questions, and must belong to the population of Messiwa. The questionnaire included two parts, the first one was the personal information of the informant (age, sex, and place of birth), and the second part was the list of medicinal and aromatic plants (MAP) used before and during the pandemic.

The medicinal plants taken into consideration were those mentioned by at least three informants. These plants were collected in the field with the presence of local persons before being identified by one of the co-authors in the herbarium of the Faculty of Sciences Semlalia, Cadi Ayyad University, Marrakech. Moreover, a bibliographical search was performed to determine the main phytochemicals of essential oils and the extracts of the cited plants.

Main protease (M^{pro}) preparation

Molecular docking was performed by the resolved crystal structure of the COVID-19 main protease (M^{pro}) in complex with the N3 inhibitor (Jin et al., 2020) obtained from the RCSB PDB (2020) database (PDB code: 6LU7). In the process, the protein was prepared using AutoDockTools; water molecules were removed, polar hydrogens and Kollman charges were added (da Silva et al., 2020), and the result was saved in PDBQT format.

Ligands preparation

The main phytochemicals of the extracts and the essential oils of the cited plants were explored based on the bibliography. The 3D structures of these molecules were extracted from the PubChem database in SDF format and were converted into PDB files using PyMOL software (Borrel and Fourches, 2017). All generated structures were prepared using AutoDockTools version 1.5.6, and the results were saved in PDBQT format (Seeliger and de Groot, 2010).

Molecular docking

AutoDock Vina, was used to assessing the binding affinity of the phytochemicals to the M^{pro} (Forli et al., 2016). The binding conformation of ligands with the lowest binding affinity was characterized as the most stable conformation of the ligands with respect to the receptor (Ahmad et al., 2021). The grid was defined to cover the SARS-CoV-2 M^{pro} active site. The grid size and the spacing value were respectively 40 Å × 40 Å × 40 Å and 0.375 Å. The grid center coordinates were -26.283, 12.599, 58.965 (XYZ assignments, respectively). Discovery Studio Visualizer was subsequently used to prepare the docked poses and 2D interaction patterns.

Statistical analysis

The citation number of each species, the characteristics of the studied population, and all the statistical analyses were performed using the Excel 2010 and SPSS 20 software for Windows version 10.0.5.

RESULTS AND DISCUSSION

The structure of interviewed population

All participants are natives of the Al-Haouz region, adults, and able to answer our questions. Out of the 85 individuals who responded to the survey, 34 were women, and 51 were men. The mean age of this population was 51 years (the minimum was 32 years, and the maximum was 82 years old).

The cited species characteristics

In this survey, our informants had cited 11 aromatic and medicinal plants. These plants are known in the Al-Haouz region as being used for cold-weather illnesses; hence their use against cold, flu, and recently against COVID-19 (El Alami et al., 2020).

According to Table 1, the *Lamiaceae* family was the most represented by 10 species while the *Compositae* family had only one cited species, *Artemisia herba-alba* Asso. Furthermore, all these plants could be used as herbal tea; the technique adopted for *Artemisia herba-alba* Asso was the decoction while the infusion was applied for the remaining 10 species. *Mentha suaveolens* Ehrh. and *Ajuga iva* (L.) Schreb. could be used to garnish other meals such as soup, bread or in the famous Moroccan dish "couscous".

Fig. 2 shows the number of citations for each medicinal plant species used against SARS-CoV-2 contamination. The most cited species was *Thymus saturejoides* Coss. (59 citations), an endemic species of Morocco (El Bouzidi et al., 2013) belonging to the genus *Thymus* known for its antioxidant, insecticidal, antibacterial, antifungal, anti-inflammatory and antiviral

Table 1. Botanical families and medicinal uses of the cited plants.

Plant species	Botanical family	Methods of use	Medicinal uses
Ajuga iva (L.) Schreb.	*Lamiaceae*	Garniture/Infusion	Against cold and abdominal pain
Artemisia herba-alba Asso	*Compositae*	decoction	Against cold, abdominal pain and wounds
Lavandula dentata L.	*Lamiaceae*	Infusion	Against cold and abdominal pain
Lavandula mairei Humbert	*Lamiaceae*	Infusion	Against cold
Lavandula stoechas L.	*Lamiaceae*	Infusion	Against cold and good for the urinary tract
Marrubium vulgare L.	*Lamiaceae*	Infusion	Against cold, abdominal pain and wounds
Mentha pulegium L.	*Lamiaceae*	Infusion	Refreshing and anti-cold
Mentha suaveolens Ehrh.	*Lamiaceae*	Garniture/Infusion	Refreshing and anti-cold
Rosmarinus officinalis L.	*Lamiaceae*	Infusion	Against cold and abdominal pain
Thymus saturejoides Coss.	*Lamiaceae*	Infusion	Against cold and abdominal pain
Thymus willdenowii Boiss.	*Lamiaceae*	Infusion	Against cold and abdominal pain

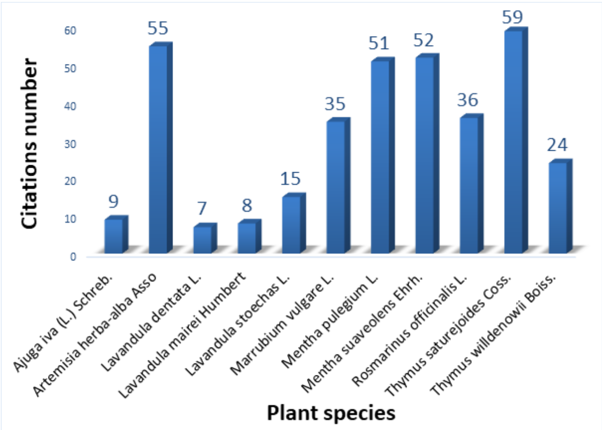


Figure 2. The citation number of the aromatic and medicinal plants.

activities (Sidali et al., 2017). El Alami et al. (2020) cited the same species in the Beni Mellal-Khenifra region as being used for the same preventive purpose against COVID-19. The main compound of *Thymus saturejoides* Coss. essential oil is borneol (Bammou et al., 2010), while hesperetin is the main component of its extract (Khouya et al., 2015). The second species of this genus was *Thymus willdenowii* Boiss. with thymol as the main component of the extract (Jaafari et al., 2007) and the essential oil, too (Ouknin et al., 2019).

Artemisia herba-alba Asso was the second most cited species (55 citations), but it remains less studied compared to other species of the same genus *Artemisia*, which accounts for more than 300 species (Gouveia and Castilho, 2013). One of the most studied species of this genus is the Chinese species *Artemisia annua* inhibitor of the enzymatic activity of chymotrypsin-like protease (CLPro), which is an enzyme produced by SARS-CoV-2 (Law et al., 2020). In addition, *Artemisia herba-alba* Asso (Table 2) shows vanillic acid as the main compound of its extract (Boukhennoufa et al., 2020) and the camphor as the main compound of its essential oil (Paolini et al., 2010).

The genus *Mentha* was represented by two species: *Mentha suaveolens* Ehrh. and *Mentha pulegium* L., which have a wide range of bioactive molecules. Concerning *Mentha pulegium* L. The main compound of its extract is gallocatechin (Taamalli et al., 2015), while the main compound of its essential oil is the pulegone (Boukhebti et al., 2011) which is an effective antiviral agent with the potential to inhibit the SARS-CoV-2 spike protein (Kulkarni et al., 2020). Moreover, *Mentha suaveolens* Ehrh. (Table 2) presents rosmarinic acid as the main compound in its extract (Bichra and Benkhalti, 2012), while the main compound in its essential oil is piperitenone oxide (Božović et al., 2015), also known as a potential inhibitor of the main protease of SARS-CoV-2 (Muhammad et al., 2020).

Rosmarinus officinalis L. presents interesting therapeutic properties due to its phytochemicals, mainly carnosic acid, carnosol and rosmarinic acid (Andrade et al., 2018). According to Ibrahim et al. (2020), the three metabolites of *Rosmarinus officinalis* L. that are potential inhibitors against the SARS-CoV-2 main protease were respectively; carnosol, baicalin and carnosic acid. In addition, the main compound of its extract is the carnosic acid (Herrero et al., 2010) and the α-pinene is the main compound of its essential oil (Szumny et al., 2010).

According to many studies, *Marrubium vulgare* L. has a high bioactive potential (Aćimović et al., 2020). Its antimicrobial activity, particularly antiviral, has been recorded (Amal Gaber et al., 2014). Moreover, the β-bisabolene is the main compound in the essential oil of *Marrubium vulgare* L. (Hamdaoui et al., 2013). On the other hand, marrubiin, which is the main compound of the extract (Stulzer et al., 2006), was evaluated for the first time through this article as a potential inhibitor of the main SARS CoV-2 protease.

The genus *Lavendula* was represented by three species: *Lavandula dentata* L., *Lavandula stoechas* L. and *Lavandula mairei* Humbert. The main compounds of their essential oils are respectively; 1,8-cineole (Dob et al., 2005), fenchone (Hassiotis, 2010) and carvacrol (El Hamdaoui et al., 2018). In addition, the main compounds of their extracts are respectively; rosmarinic acid (Pereira et al., 2019), chlorogenic acid (Celep et al., 2018) and quercetin 3-glucuronide (Berrissoul et al., 2020).

Regarding the *Ajuga iva* (L.) Schreb. species, commonly used in Africa to treat several diseases such as metabolic disorders, digestive and respiratory disorders (Bouyahya et al., 2020). The main compound of its essential oil is dienestrol (Chouitah et al., 2017), whereas cyasterone is the main compound of its extract (Bouyahya et al., 2020). Moreover, the cyasterone was also evaluated for the first time through this article as a potential inhibitor of the main SARS CoV-2 protease.

Tables 2 shows the 2D structures and the affinities for the main compounds of the extracts and the essential oils of the 11 cited species. The affinity range for the main phytochemicals of the extracts was from -7.7 kcal/mol to -4.9 kcal/mol, and the affinity range for the main phytochemicals of the essential oils was from -6.6 kcal/mol to -4.6 kcal/mol. The phytochemicals in the extracts showed a higher inhibitory potential than the phytochemicals in the essential oils. Moreover, the rosmarinic acid (-7.7 kcal/mol), hesperetin (-7.2 kcal/mol), gallocatechin (-7.2 kcal/mol) and cyasterone (-7.2 kcal/mol) showed a higher inhibitory potential against COVID-19 M^{pro}, respectively. Furthermore, the binding locations of the four phytochemicals in the active site of M^{pro} are shown in Fig. 3.

Figure 4 shows the amino acid residues that interact with these four ligands within the protein pocket as well as their interaction types. The superior potential of these four phytochemicals as inhibitors of M^{pro} was attributed to their ability to form multiple hydrogen bonds and other non-covalent interactions with key amino acids within the active site (Fig. 4). In particular, the rosmarinic acid (-7.7 kcal/mol) was the compound with the highest inhibition potential. This compound formed 4 hydrogen bonds with four amino acids (Thr111, Asn151, Gln110 and Lys102), a Pi-Sigma interaction (with Val104) and a Pi-Pi Stacked bond (with Phe294).

Table 2. The main phytochemicals of the essential oils and the extracts from the cited plants and their binding affinity against the M^{pro}.

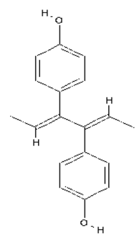
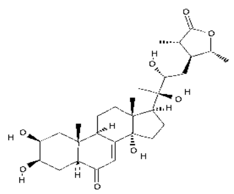
Plant species	Main compound		Affinity (kcal/mol)	Binding residues
Ajuga iva (L.) Schreb.	Essential oil (Chouitah et al., 2017)	 Dienestrol (PubChem ID: 667476)	-6.6	Phe294, Ser158, Val104, Ile106
	Extract (Bouyahya et al., 2020)	 Cyasterone (PubChem ID: 119444)	-7.2	Pro184, Glu240, Thr198, Thr196, Pro108

Table 2. The main phytochemicals of the essential oils and the extracts from the cited plants and their binding affinity against the M^{pro} *(continued…)*

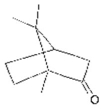
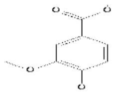
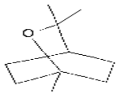
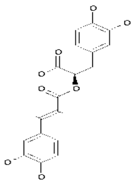
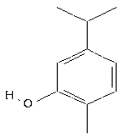
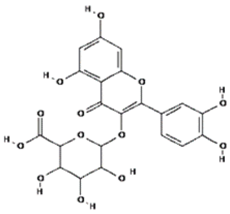
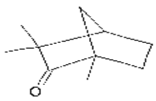
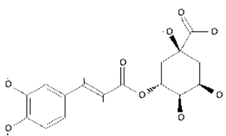
Plant species	Main compound	Affinity (kcal/mol)	Binding residues
Artemisia herba-alba Asso	Essential oil (Paolini et al., 2010)  Camphor (PubChem ID: 2537)	-4.8	Phe294, Phe8
	Extract (Boukhennoufa et al., 2020)  Vanillic acid (PubChem ID: 8468)	-5.3	Ile106, Asp295
Lavandula dentata L.	Essential oil (Dob et al., 2005)  1,8-Cineole (PubChem ID: 2758)	-5.1	Phe294
	Extract (Pereira et al., 2019)  Rosmarinic acid (PubChem ID: 5281792)	-7.7	Thr111, Asn151, Gln110, Phe294, Val104, Lys102
Lavandula mairei Humbert	Essential oil (El Hamdaoui et al., 2018)  Carvacrol (PubChem ID: 10364)	-5.1	Thr111
	Extract (Berrissoul et al., 2020)  Quercetin 3-glucuronide (PubChem ID : 12004528)	-6.9	Tyr239, Leu286, Asp289, Glu290, Thr199, Asn238, Lys137
Lavandula stoechas L.	Essential oil (Hassiotis, 2010)  Fenchone (PubChem ID: 14525)	-5.3	Phe294
	Extract (Celep et al., 2018)  Chlorogenic acid (PubChem ID: 1794427)	-7.1	Gly143, Leu141, Ser144, His163, Arg188, Thr190

Table 2. The main phytochemicals of the essential oils and the extracts from the cited plants and their binding affinity against the M^{pro} *(continued…)*

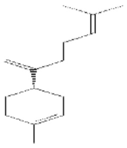
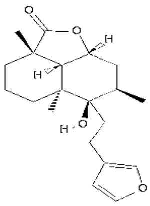
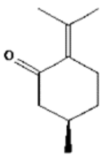
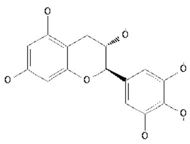
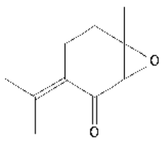
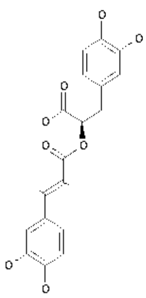
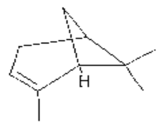
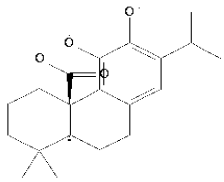
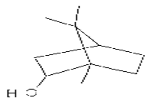
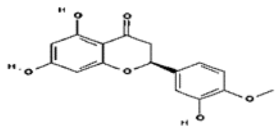
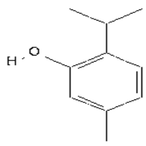
Plant species	Main compound		Affinity (kcal/mol)	Binding residues
Marrubium vulgare L.	Essential oil (Hamdaoui et al., 2013)	 β-bisabolene PubChem ID : 10104370	-6.1	Phe294, Ile106, Val104
	Extract (Stulzer et al., 2006)	 Marrubiin (PubChem ID: 73401)	-6.9	Ile106, Asn151
Mentha pulegium L.	Essential oil (Boukhebti et al., 2011)	 Pulegone (PubChem ID: 442495)	-5.0	Gln110, Val104, Ile106, Phe294
	Extract (Taamalli et al., 2015)	 Gallocatechin (PubChem ID: 65084)	-7.2	Arg188, Cys145, Gly143, Leu141
Mentha suaveolens Ehrh.	Essential oil (Božović et al., 2015)	 Piperitenone oxide (PubChem ID: 61942)	-5.4	Phe294, Thr111, Val104
	Extract (Bichra and Benkhalti, 2012)	 Rosmarinic acid (PubChem ID: 5281792)	-7.7	Thr111, Asn151, Gln110, Phe294, Val104, Lys102

Table 2. The main phytochemicals of the essential oils and the extracts from the cited plants and their binding affinity against the M^{pro} *(continued…)*

Plant species	Main compound	Affinity (kcal/mol)	Binding residues
Rosmarinus officinalis L.	Essential oil (Szumny et al., 2010)  α-Pinene (PubChem ID: 6654)	-4.9	Lys5, Phe3, Trp207, Leu282, Phe291
	Extract (Herrero et al., 2010)  Carnosic acid (PubChem ID: 65126)	-6.5	Glu166, His41
Thymus saturejoides Coss.	Essential oil (Bammou et al., 2010)  Borneol (PubChem ID: 64685)	-4.6	Lys5, Phe291, Leu282
	Extract (Khouya et al., 2015)  Hesperetin (PubChem ID: 72281)	-7.2	His41, Met49, His163, His172, Gln189, Met165
Thymus willdenowii Boiss.	Essential oil (Ouknin et al., 2019) Extract (Jaafari et al., 2007)  Thymol (PubChem ID: 6989)	-4.9	Phe291, Trp207, Lys5

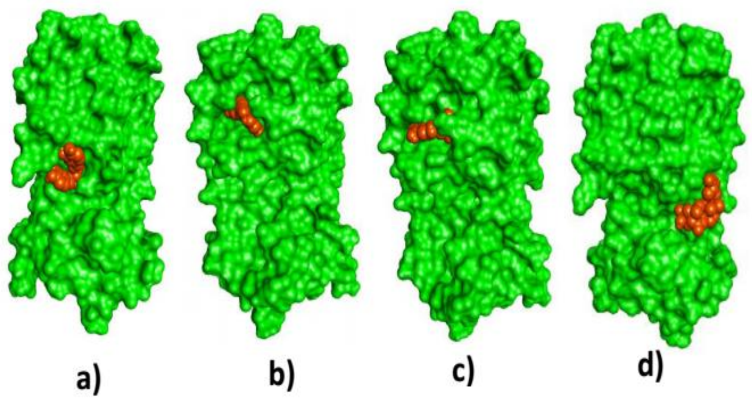


Figure 3. Docking structure of M^{pro} in complex with the four phytochemicals.
a) Rosmarinic acid, **b)** Hesperetin, **c)** Gallocatechin, **d)** Cyasterone.

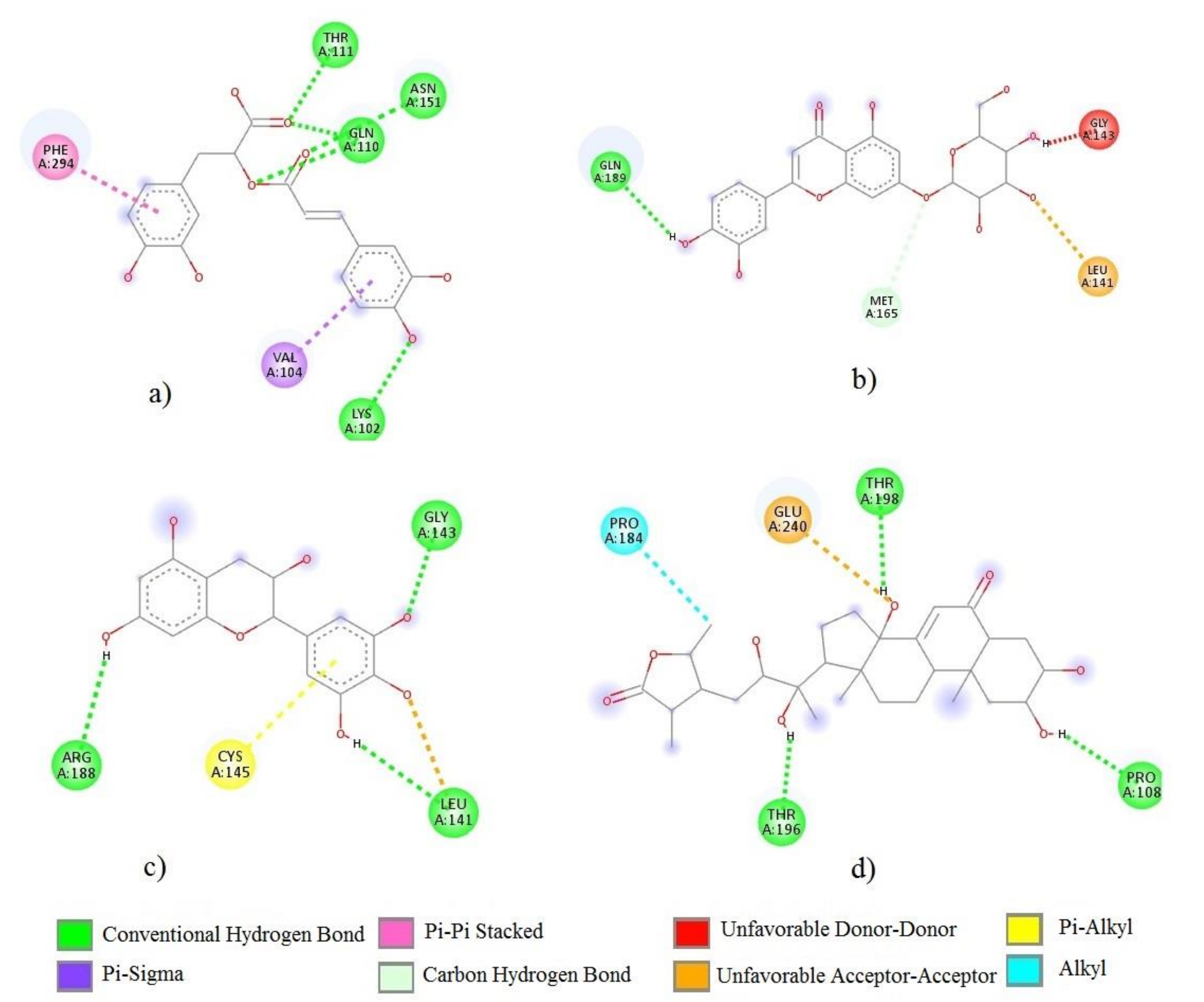


Figure 4. Representations of the interactions of the four phytochemicals.
a) Rosmarinic acid, **b)** Hesperetin, **c)** Gallocatechin, **d)** Cyasterone, with the amino acid residues of SARS-CoV-2 main protease

Limitations

This study was conducted within a part of Morocco (Central High Atlas Mountains) and may not necessarily reflect all the factors influencing the low contamination rate in this study area.

CONCLUSION

The COVID-19 pandemic causes a public health crisis. The management of this situation requires comprehensive cooperation in order to optimize costs and save time. Hence, the importance of the ethnomedicinal and the *in silico* studies to evaluate already approved drugs and different phytochemicals against SARS-CoV-2. It is within this framework that our study evaluated by the virtual screening the inhibitory potential of the main phytochemicals contained in the cited plants. These phytochemicals have shown a higher inhibitory potential against COVID-19 Main protease (M^{pro}). Therefore, it is mandatory to evaluate *in vivo* and *in vitro* of these phytochemicals that are shown to be promising against this pandemic.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Ghanimi R	Ouhammou A	El Atki Y	Cherkaoui M
Concepts or ideas	x			x
Design	x			
Definition of intellectual content	x			
Literature search	x			
Experimental studies	x			
Data acquisition	x	x		x
Data analysis	x			x
Statistical analysis	x			
Manuscript preparation	x	x	x	x
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

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