Ethnobotanical survey on plants used by traditional healers to fight against COVID-19 in Fez city, Northern Morocco

Nesrine Benkhaira, Saad Ibnsouda Koraichi and Kawtar Fikri-Benbrahim

Research

Abstract

Background: Coronavirus disease 2019 (COVID-19) has now been spread around the world in the form of a highly contagious pandemic. The lack of effective vaccines against this lethal viral infection is pushing researchers to identify potential sources from natural products that can help fight the pandemic. In Morocco, medicinal and aromatic plants (MAPs) have long been used to combat infectious diseases. According to our knowledge, this is the first ethnobotanical survey in Fez city, aimed to quantify the ethnobotanical knowledge of medicinal plants used by herbalists for fighting against the COVID-19.

Methods: An ethnobotanical survey was conducted in Fez city with traditional herbalists, in a period of two months (from the beginning of November to the end of December 2020). Semi-structured interviews were conducted with 50 well-known traditional herbalists. A quantitative analysis approach was used resulting in the determination of plant use value (PUV) and family use value (FUV) to evaluate the ethnobotanical knowledge.

Results: In total, 49 medicinal plants species were recorded belonging to 28 botanical families. According to the PUV index, the most important species were *Syzygium aromaticum* (L.) Merr. & Perry, *Thymus vulgaris L.*, *Eucalyptus globulus* Labill., *and Artemisia vulgaris* L. The Lamiaceae was the most dominant family. The aerial part was the most used plant part. Most remedies were prepared in the infusion form and mostly administered orally. According to herbalists, 47.36 % of customers were very satisfied using herbal remedies to combat COVID-19.

Conclusion: The ethnobotanical and ethnopharmacological information collected in our study provides basic data on medicinal plants which is promising in the treatment and prevention of COVID-19. Thus, it is recommended that the safety and efficacy of these plants will be confirmed through pharmacological, toxicological and phytochemical studies.

Keywords: Covid-19, medicinal plants, traditional medicine, ethnobotany, Fez, Morocco.

Correspondence

Nesrine Benkhaira, Saad Ibnsouda Koraichi, Kawtar Fikri-Benbrahim

Laboratory of Microbial Biotechnology and Bioactive Molecules, Sciences and Technologies Faculty, Sidi Mohamed Ben Abdellah University, B.P. 2202 Imouzzer Road, Fez, Morocco

*Corresponding Author: kawtar.fikribenbrahim@usmba.ac.ma

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Résumé

Contexte: Actuellement, la maladie à coronavirus 2019 (COVID-19) s'est propagée dans le monde entier sous forme d'une pandémie hautement contagieuse. Le manque de vaccins efficaces contre cette infection virale et mortelle pousse les chercheurs à identifier des sources potentielles de produits naturels qui peuvent aider à lutter contre la

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pandémie. Au Maroc, les plantes médicinales et aromatiques sont utilisées depuis longtemps pour lutter contre les maladies infectieuses. Selon nos connaissances, il s'agit de la première enquête ethnobotanique dans la ville de Fès, visant à quantifier les connaissances ethnobotaniques des plantes médicinales utilisées par les herboristes pour lutter contre le COVID-19.

Méthodes: Une enquête ethnobotanique a été menée dans la ville de Fès auprès des herboristes traditionnels, sur une période de deux mois (du début Novembre à la fin de Décembre 2020). Des entretiens semi-structurés ont été menés avec 50 herboristes traditionnels bien connus. Une approche d'analyse quantitative a été utilisée pour déterminer la valeur d'usage des plantes (PUV) et la valeur d'usage familial (FUV) pour évaluer les connaissances ethnobotaniques.

Résultats: Au total, 49 espèces de plantes médicinales, appartenant à 28 familles botaniques, ont été enregistrées. Selon l'indice PUV, les espèces les plus importantes étaient *Syzygium aromaticum* (L.) Merr. & Perry, *Thymus vulgaris* L., *Eucalyptus globulus* Labill. et *Artemisia vulgaris* L. La famille des Lamiaceae était la plus dominante. La partie aérienne représentait la partie la plus utilisée des plantes. La plupart des remèdes était préparée sous forme d'infusion et principalement administrée par voie orale. Selon les herboristes, 47,36% des clients étaient très satisfaits d'utiliser des remèdes à base de plantes pour lutter contre le COVID-19.

Conclusion: Les informations ethnobotaniques et ethnopharmacologiques collectées dans notre étude fournissent des données de base sur les plantes médicinales qui semblent prometteuses dans le traitement et la prévention du COVID-19. Ainsi, il est recommandé que l'innocuité et l'efficacité de ces plantes soient confirmées par des études pharmacologiques, toxicologiques et phytochimiques.

Mots clés: COVID-19, plantes médicinales, médecine traditionnelle, ethnobotanie, Fès, Maroc.

Background

In December 2019, several cases of pneumonia were reported in Wuhan city, Hubei province, China. The causative agent was confirmed as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), previously named 2019 novel coronavirus (2019-nCoV) (WHO 2020). As of April 2020, the virus was rapidly transmitted between humans through direct contact. The virus has spread approximately causing a worldwide pandemic in more than 200 countries (Platto *et al.* 2020). Recently, in January 2021, the World health organization reported more than 90 million confirmed cases and more than two million deaths (WHO 2021a). The disease was termed COVID-19. It is characterized by fever, dry cough, dyspnea, and diarrhea. In severe cases, the symptoms are pneumonia, metabolic acidosis, septic shock, and bleeding (Yi *et al.* 2020).

In Morocco, the first confirmed case was reported on the 2nd March 2020 concerning a Moroccan man returning from Italy. More recently, Morocco has recorded a number exceeding 400.000 confirmed cases, and more than 7.000 deaths (WHO 2021b). Concerning Fez city, the first case of COVID-19 appeared on March 11st 2020. It was about a woman of Senegalese origin, having 64 years old, who arrived in Fez from France on March 5th. Currently, the Fez-Meknes region has a total number of more than eight hundred confirmed cases of which Fez city often record the highest number of new cases per day (Ministère de la Santé 2021).

To date, several control measures are being instituted around the world to control the spread of the disease including strict quarantine measures, personal hygiene, and development of vaccines such as live attenuated vaccines, vectors of adenovirus, recombinant proteins, and nucleic acid (DNA and mRNA) (Güner *et al.* 2020, Holmes 2003). However, no vaccine has been approved to be 100% effective against the SARS-CoV-2 so far (Oladele *et al.* 2020). Today, the pandemic becomes the most frightening and terrifying issue causing high health impact and huge economic losses around the world (UNIDO 2020).

Therewith, the pharmaceutical industry and scientific research are focusing on exploration of natural products particularly, MAPs producing several bioactive molecules approved effective against viral infections, including those from coronaviruses, enterovirus, hepatitis B, hepatitis C, herpes simplex virus (HSV), human immunodeficiency (HIV), and influenza viruses (IFV) (Monticolo *et al.* 2020).

Moreover, essential oils (EOs) from aromatic herbs, were also found to be active against a wide variety of viruses, such as IFV, HSV, HIV, yellow fever virus, and avian influenza (Asif *et al.* 2020). Therefore, MAPs and EOs could be a better option to product novel antiviral drugs that can be effective against the SARS-CoV-2 (Boukhatem & Setzer 2020).

Furthermore, traditional healers have played a vital role in the fight against many ailments through using plants as natural remedies without even knowing their bioactive molecules. While today's researchers are especially interested in bioactive molecules extracted from plants to apply them in the fight against the current pandemic (Asif *et al.* 2020).

In this context, our study aims to collect information on herbal remedies employed to fight against the COVID-19, in Fez city, by herbalists and traditional healers who possess valuable knowledge about medicinal plants, in order to valorize the MAPs and to perform basic data that will contribute to overcoming the pandemic. This is the first ethnobotanical investigation in Fez city, aimed to quantify the ethnobotanical knowledge of medicinal plants used by herbalists for fighting against the COVID-19.

Material and methods

Description of the study area

This study was carried out in Fez, the cultural and spiritual capital of Morocco. Fez is a city in northern inland Morocco, located to the northeast of the Atlas Mountains (34° 2′ 36″ N, 5° 0′ 12″ W). Fez connects the important cities of different regions; 206 km from Tangier to the northwest, 246 km from Casablanca and 189 km from Rabat to the west, and 387 km from Marrakesh to the southwest which leads to the Trans-Saharan trade route ("Morocco (IFMSA-Morocco) - Fez" n.d.).

Fez is divided between the old Fez (Fez el-bali) and the new Fez (Fez el-jedid) (Fig. 1). Further south is the town of Sefrou, and further southwest is the city of Meknes. The prefecture of Fez covers an area of 312 km. Its urban commune is divided into six districts: Agdal, Saïss, Fez-Medina, Jnan El Ouard, El Mariniyine, and Zouagha. Fez covers 280 hectares with a population of 1.22 million, it is the second largest city in Morocco after Casablanca (Aouchar 2005, Cherkaoui *et al.* 2017).

Fez has a mild and sunny Mediterranean climate. The highest and lowest temperatures ever reported are 46.7 °C and −8.2 °C, respectively. The winter highs typically reach around 15 °C in December-January. During summer, the average temperature is about 32 °C. The climate of Fez city is similar to that of Cordoba (Climatological Information for Fez, Morocco 2011).

The economy of the local population of Fez city is mainly based on tourism, agriculture and handicraft. The rural area surrounding the city and the fertile plains of Saïss represent an important source of producing cereals, beans, olives, and grapes. Moreover, there are two natural parks which constitute the vegetal richness of the city: the Tazeka Park, to the northeast, and the Ifrane national park covering more than 500 km^2 and including the largest cedar forest in Morocco (UNESCO n.d.).

Data collection

In order to gather information on MAPs used for curing and preventing the COVID-19, an ethnobotanical and ethnopharmacological survey was conducted from November 1st to December 31st, 2020. During this period different districts of Fez city were visited (Fig. 1).

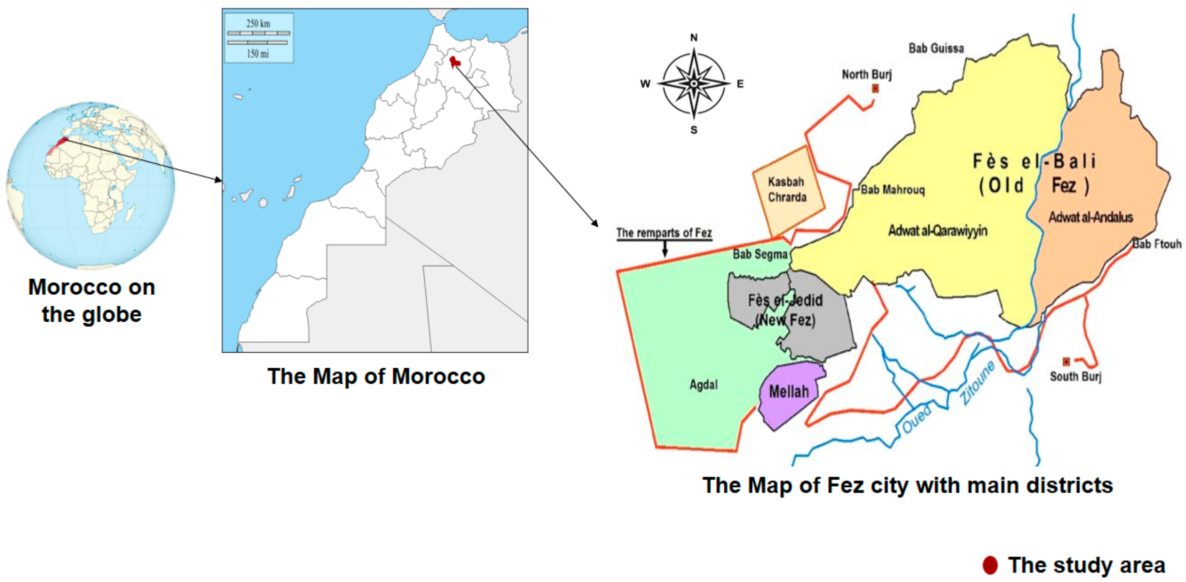

Figure 1. Location of the study area; Fez-Morocco.

To collect data, a semi-structured questionnaire was prepared, and information were compiled through face-to-face interviews with herbalists and traditional healers. This method was chosen as it is very convenient for data collection (Jaradat *et al.* 2017). The questionnaire was divided into two parts; the first concerned the socio-demographic profile of herbalists (age, gender, level academic, and experience years) and the second part was about the MAPs used to fight against the COVID-19 (local, scientific and family names, the part used, preparation modes, posology etc.).

A total of 50 traditional herbalists, including 43 male and 7 female aged between 27 and 76 years, were selected randomly from different districts of Fez city and interviewed. Most of the herbalists were in the region of Fes el-bali (the old medina of Fez) where the inhabitants mainly depend on traditional medicine for healthcare because of the high cost of modern medicine and the low social level of the old medina inhabitants. The aim of our study was clarified to herbalists to maintain transparency and to obtain reliable answers for scientific purposes and not for commercial ones. The interviews with herbalists were conducted in the local language (Arabic) in a period ranging from 20 to 40 minutes by each of them. Then, all documented data were translated into English.

Identification of the species

The species were initially identified by their local names, then validated through special botanical books to know: Medicinal plants of Morocco (Sijelmassi 1993), Practical flora of Morocco: manual for the determination of vascular plants (Fennane *et al.*1999), Catalogs of vascular plants of northern Morocco with identification keys (Valdés 2002).

Other standard Moroccan floras were used to ensure identification: The traditional Moroccan pharmacopoeia: ancient Arabic medicine and popular knowledge (Bellakhdar 1997) and Moroccan medicinal and aromatic plants (Hmamouchi 1999). Some botanical databases were also used to confirm the taxonomic names of our species, encyclopedia of Life and The Plant List.

Moreover, the medicinal plants recorded in our work were compared to those reported in ethnobotanical surveys carried out in the same study area (Jouad *et al.* 2001, Mikou *et al.* 2016, Youbi *et al.* 2016) as well as in other regions of Morocco (Chaachouay *et al.* 2019, El Hachlafi *et al.* 2020, Haouari *et al.* 2018, Harouak *et al.* 2018, Najem *et al.* 2020, Strathern 2002).

Data analysis

Data collected in our study were statistically analyzed using SPSS (System Package for Social Sciences, version 21) and Microsoft Office "Excel 2013". Data concerning socio-demographic profile of herbalists were examined by a simple descriptive statistical method using percentages and frequencies. Whereas the ethnobotanical and ethnopharmacological data were analyzed using quantitative value indices; The FUV and PUV.

The Family Use Value (FUV)

The FUV was assessed to determine the significance of medicinal plant families. This index is used in ethnobotany to determine a value of a biological plant taxon. The FUV was calculated according to the following equation (Sreekeesoon & Mahomoodally 2014):

$$FUV = UVs / (ns)$$

Where: UVs refers to the use values of the taxa and ns to the total number of species within each family.

Plant Use Value (PUV)

The PUV is a quantitative method, demonstrating the relative importance for each species known locally. The PUV was determined according to the following equation (Trotter & Logan 1986):

$$PUV = U/N$$

Where: U refers to the number of citations per species and N to the number of herbalists interviewed. A high PUV indicates the potential importance of the plant species reported.

Review study

In order to confirm the ethnobotanical and ethnopharmacological information obtained in our study, a literature review was performed about antiviral and immunomodulatory properties of the medicinal plants most recommended by herbalists for preventing and treating the COVID-19 (species with the highest PUV).

A literature review was conducted by a systematic search of the scientific literature using Pubmed, Scopus, and Google Scholar. The following Keywords were used to facilitate the collection of data: individual plant names, “COVID-19” OR “coronavirus” OR “SARS-CoV-2” AND “antiviral” AND “immunomodulatory”. The PubChem database and the software ChemDraw Ultra 12.0 were used to draw the chemical structures.

Results and discussion

Socio-demographic profile of herbalists

Gender

In total, 50 herbalists including 86% of men and 14% of women were interviewed. The predominance of men can be explained by the fact that in our society men work to provide favorable conditions for their families while most women care for their family and manage household affairs. Other ethnobotanical studies recently carried out on a national scale; Taza, Rabat-Sale-Kenitra region, Casablanca, Beni Mellal-Khenifra region, and Meknes city are concordant with our results (Bourhia *et al.* 2019, El alami *et al.* 2020, El Hachlafi *et al.* 2020, Haouari *et al.* 2018). Other international ethnopharmacological surveys carried out at Algeria, Palestine, and Saymour are also in agreement with our data (Boudjelal *et al.* 2013, Buwa-Komoren *et al.* 2019, Jaradat *et al*. 2017).

Age

In the study area, most herbalists were older than 60 years old (34%) followed by those who were between 51 and 60 years (32%), while the two age groups {31-40} and {41-50} were equal (14% for each group). Herbalists with an age less than 30 came in last position (6%). The predominance of elderly herbalists is due to the heritage of the parents' profession. These data are similar to those obtained in the ethnobotanical survey carried out in Rabat-Sale-Kenitra Region and in Lwamondo, Limpopo province of South Africa (El Hachlafi *et al.* 2020, Mahwasane *et al*. 2013).

Education level

Regarding the education level, 40% of herbalists had a primary level followed by 28% with a secondary level. While 18% were illiterate and 14 % had a university degree. These data can be explained by the fact that the practice of herbalism is inherited from ancient generations and does not require a diploma. This is in agreement with the ethnopharmaco-botanical study conducted in Sulaymaniyah Province of Irak which reported that 33% of herbalists had a primary school degree (Ahmed 2016). Other ethnobotanical surveys carried out in Morocco (Meknes and Taza) documented that most herbalists had a secondary level followed by a primary level (Harouak *et al*. 2018, Haouari *et al.* 2018). Whereas, it was reported that the majority of herbalists in Rabat-Sale-Kenitra region and North Algeria were illiterate (Boudjelal *et al.* 2013, El Hachlafi *et al.* 2020).

Years of experience in herbalism

Half of the herbalists (50%) had more than 20 years of experience, followed by 34% who had 11 to 20 years of experience, while only 16% practiced herbalism for one to 10 years. This can be explained by the fact that our study has been dominated by elderly herbalists having therefore a long experience. This also means that herbalism is in great demand from the Moroccan population. This is in agreement with the survey carried out in west bank Palestine which documented that most of herbalists had an experience over than 20 years (Jaradat *et al.* 2017). While in Taza city, the majority were reported to have an experience between 11 to 20 years (Haouari *et al.* 2018).

Quantitative analysis

Species families and their FUV

A total of 49 species belonging to 28 botanical families were recommended by herbalists to fight against COVID-19. The scientific names of species and their families, local names, the plant's part used, type, condition, preparation and administration modes, PUV, and FUV of the 49 species were detailed in Table 1. According to the number of species, the most representative families were Lamiaceae (12.5 %) followed by Asteraceae (11 %), Apiaceae (7.5 %), and Zingiberaceae (5.5 %). The remaining families were represented by a percentage ranging from 2 % to 4 % (Fig. 2 (a)). In terms of the FUV index, the most cited families are Punicaceae (FUV=1), followed by Amaryllidaceae and Lauraceae having the same FUV (0.212), and Urticaceae (FUV=0.125) (Table 1).

The dominance of these families can be explained by their extensive distribution in Morocco due to its ecological factors favoring the vegetation of the species belonging to these families. Likewise, these families are widely requested by the Moroccan population for the potential of their plant species, especially the Lamiaceae family which includes many aromatic plants producing EOs with powerful properties. Another ethnobotanical study performed in Beni Mellal-Khenifra about medicinal plants used for the prevention of COVID-19 pandemic showed that the Lamiaceae was also the most important family in the data collected (El alami *et al.* 2020). Furthermore, the ethnobotanical survey carried out in Seksaoua region (Western High Moroccan Atlas) about plants used in the treatment of respiratory diseases recorded that Lamiaceae, Apiaceae, and Asteraceae were the most dominant families. Moreover, the study executed in Rabat-Kenitra-Sale region showed that the families Lamiaceae, Asteraceae, and Apiaceae were the most cited to treat chronic diseases (El Hachlafi *et al.* 2020).

Table 1. Medicinal plants used to treat and prevent COVID-19.

Scientific names of species and families	Local name	PPU	Type	Condition	Pr. mode	Ad. mode	PUV	FUV
Amaryllidaceae								0.212
Allium cepa L.	Basla	Bu	Cl	F	Cd, J	OA	0.14	
Ammodaucus leucotrichus Coss.	Kamoun soufi	AP	Sp	D	If, Pd	OA	0.08	
Cuminum cyminum L.	Lkamoun	S	Cl	D	Pd, If	OA	0.04	
Petroselinum crispum (Mill.) Fuss	Maadnouse	AP	Sp	D	If, Dc, Pd	OA	0.12	
Pimpinella anisum L.	Ennafaa	S	Im	D	Pd, Dc, If	OA	0.1	
Apiaceae								0.002
Apium graveolens L.	Lkrafes	AP	Sp	F, D	Cd, Pd	OA	0.06	
Araliaceae								0.008
Panax ginseng C.A. Mey.	Jinsing	R	Im	D	Pd, Dc	OA, In	0.16	
Arecaceae								0.0012
Phoenix dactylifera L.	Tmar	Fr	Cl, Im	D	Rw	OA	0.06	
Asteraceae								0.001
Artemisia vulgaris L.	Chih	L	Cl	D	Dc, EO, Fm	In, OA	0.36	
Artemisia absinthium L.	Chiba	AP	Sp	D, F	Dc, If, Fm	In, OA	0.06	
Chamaemelum nobile (L.) All.	Babounj	AP	Sp	D	If	OA	0.08	
Saussurea costus (Falc.) Lipsch.	Kist hindi	R	Im	D	EO, Pd, Dc	In, OA	0.08	
Brassicaceae								0.003
Brassica rapa L.	Laft	R	Cl	F	Cd	OA	0.06	
Lepidium sativum L.	Hab errachad	S	Imp	D	If, Rw	OA	0.12	
Capparaceae								0.003
Capparis spinosa L.	Lkabbar	Fl.B	Sp	D	If, Dc	OA	0.04	
Fabaceae								0.002
Glycyrrhiza glabra L.	Arq souss	R	Im	D	Pd, If, Dc	OA	0.08	

Iridaceae								0.002
Crocus sativus L.	Zaafaran lhor	St	Sp	D	If	OA	0.06	
Juglandaceae								0.06
Juglans regia L.	Gargaa	Fr	Cl	F, D	Rw	OA	0.06	
Lamiaceae								0.013
Lavandula angustifolia Mill.	Lkhzama	AP	Sp	D	If, EO, Fm, Dc	OA, In	0.2	
Mentha pulegium L.	Fliou	AP	Sp	D, F	If, Dc, EO	OA, In	0.24	
Mentha spicata L.	Naanaa	AP	Sp	D	If, EO, Dc	OA, In	0.1	
Origanum majorana L.	Mardaddouche	AP	Cl	D	If, EO, Fm	OA, In	0.08	
Rosmarinus officinalis L.	Azir	AP	Sp	D	If, EO, Fm, Dc	OA, In	0.24	
Salvia officinalis L.	Salmia	AP	Sp	D	If, EO, Fm, Dc	OA, In	0.1	
Thymus vulgaris L.	Zaatar	AP	Sp	D	If, Dc, Pd, EO	OA, In	0.46	
Lauraceae								0.212
Cinnamomum verum J. Presl	Lqarefa	B	Im	D	Pd, Dc, If, EO	OA, In	0.22	
Laurus nobilis L.	Wraq sidna moussa	L	Sp	D	If, Dc	OA, In	0.02	
Linaceae								0.02
Linum usitatissimum L.	Zriaat lkttan	S	Cl	D	If	OA	0.06	
Meliaceae								0.007
Azadirachta indica A. Juss.	Neem	L, Fl, S	Cl	D	If, Dc	OA	0.08	
Myrtaceae								0.014
Eucalyptus globulus Labill.	kalyptous	L	Sp	D	Dc, If, EO	In, OA	0.4	
Syzygium aromaticum (L.) Merr. & Perry.	Qronfel/Oud nouwar	Fl.B	Im	D	If, EO	In, OA	0.46	
Oleaceae								0.007
Olea europaea L.	Zitoun	L, Fr	Sp	F	If, Dc, M, VO	OA	0.12	
Piperaceae								0.002
Piper nigrum L.	Ibzar	Fr	Im	D	Pd	OA	0.04	

Poaceae								0.001
Avena sativa L.	Khartal/ choufan	S	Cl	D	Rw, If, Pd	OA, Ct	0.02	
Polygonaceae								0.0008
Fagopyrum esculentum Moench	Hanta sawdae	S	Cl	D	Cd	OA	0.02	
Punicaceae								1
Punica granatum L.	Remman	Fr	Sp	F	J	OA	0.04	
Ranunculaceae								0.003
Nigella sativa L.	Habba sawdae/sanouj	S	Cl	D	Dc, If, Pd, VO	OA	0.08	
Rosaceae								0.001
*Prunus dulcis (*Mill.) D.A. Webb	Louz	Fr	Sp	F, D	Rw	OA	0.06	
Rubiaceae								0.0002
Rubia tinctorum L.	Elfoua	R	Cl	D	If, Pd	OA	0.04	
Urticaceae								
Urtica dioica L.	Harigua	AP	Sp	D	Dc, If, Pd	OA	0.04	
Zingiberaceae								0.017
Alpinia officinarum Hance	Khoudnjal	Rh	Im	D	If, Pd	OA	0.14	
Curcuma longa L.	Lkharqoum	Rh	Im	D	If, Pd	OA	0.1	
Zingiber officinale Roscoe	Zanjabil	Rh	Im	D	J, Dc, If, Pd	OA	0.2	

PPU: plant's part used; L: Leaves; Fl.B: Flower buds; Sp: Spontaneous; D: dry; F: Fresh; Dc: Decoction; If: infusion; OA: oral administration; Im: Imported; Fl: Flowers; Cl: Cultivated; Fm: fumigation; R: root; Pd: powder; AP: aerial part; Rh: rhizome; J: juice; B: Bark; Bu: bulb; Cd: cooked; Fr: fruit; M: maceration; S: seeds; Rw: raw; VO: vegetal oil; St: stigma; Ct: cataplasme; Ma: Massage; Pr: preparation; Ad: administration.

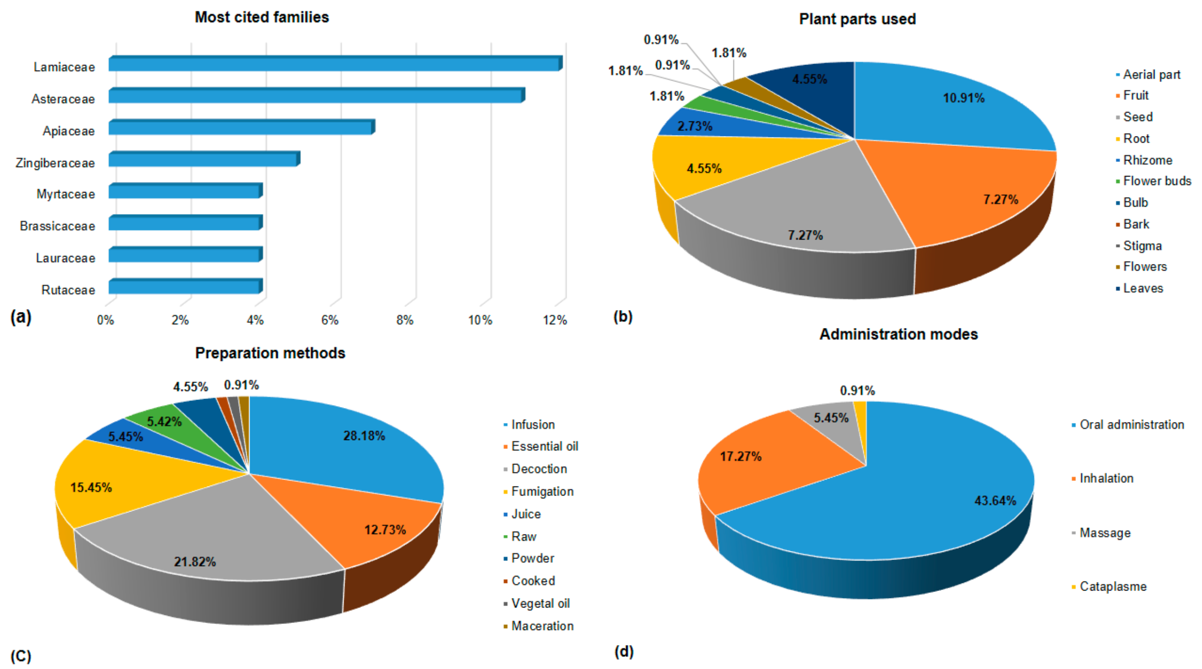

Figure 2. (a) Percentage of most cited families. (b) Percentage of the different plant parts used.(c) Percentage of different preparation methods of herbal remedies.(d) The frequency of administration modes of herbal preparations.

Medicinal plants and their PUV

The PUV index of species is calculated to evaluate the importance of medicinal plants. Data showed that the PUV of reported species ranged from 0.46 to 0.02. *Syzygium aromaticum* (L.) Merr. & Perry., and *Thymus vulgaris L.* exhibited the highest value (PUV=0.46), followed by *Eucalyptus globulus* Labill. (PUV=0.4*), Artemisia vulgaris* L. (PUV=0.36). The species *Rosmarinus officinalis* L. and *Mentha pulegium* L. had the same PUV index (PUV=0.24), followed by *Cinnamomum verum* J. Presl (PUV=0.22) (Table 1). Species with a high PUV index are the most mentioned by herbalists. Therefore, they could have important antiviral and immunostimulatory properties.

Literature review

Medicinal plants having the highest PUV indexes appear to possess promising antiviral and immunostimulatory properties. Thereupon, bibliographic research was performed aiming the scientific evidence through *in vivo* and *in vitro* studies of the plants' properties. Table 2 summarizes data collected from the literature, and Figure 3 shows the chemical structures of the main active compounds indicated in the table below.

Parts of the medicinal plants used

In general, the aerial part has been reported as the most used part by the interviewed herbalists for herbal medicine preparations (10.91%), followed by seeds (7.27%), fruits (7.27%), leaves (4.55%), and roots (4.55%). Other parts of plants (stigma, bark, flower, flower buds) come last with a percentage between 0.91 to 2.73% (Fig.2 (b)). The frequent use of aerial part is due to the availability, simplicity of harvest, and herbal medicine preparation. Moreover, the leaves store many secondary metabolites that are responsible for the biological activities of the species. Another study showed that aerial parts, seeds, and leaves were the most used in the treatment of respiratory disorders with slight differences (Sbai-Jouilil *et al.* 2017).

Methods of remedies' preparation

Several preparation modes are used to facilitate the administration of active principles of medicinal plants. Our study showed that infusion was the dominant preparation method of herbal remedies to fight against COVID-19 (28.18%). Followed by decoction (21.82%), powder (15.45%), essential oil (12.73%), and other methods of preparation (juice, fumigation, raw, cooked, vegetal oil, and maceration) ranged from 1 to 5.45% (Fig.2 (c)). The infusion is frequently used because it allows collecting the most active compounds of medicinal plants as well as it can attenuate the toxic effect of some recipes. It also prevents the destruction of certain bioactive molecules in medicinal plants. Our data are in agreement with the ethnobotanical survey of the medicinal plant used to treat metabolic disorders in Moroccan Rif (Chaachouay *et al.* 2019).

Table 2. Antiviral and immunostimulatory properties of the most cited medicinal plants.

Species	Antiviral properties	Immunostimulatory properties	Active compounds	Mechanism of action	References
Artemisia annua L.	ME obtained from the aerial parts showed a strong *in vitro* anti-herpetic activity (HSV1-infected HeLa cells)	ME and leaf powder of A. annua showed an increase performance, cellular and humoral immunity of Cobb broiler chicks	Artemisinin	Suppression of flaviviruses replication, enhancement of type I interferon response by up-regulation of key factor phosphorylation (Interferon Regulatory Factor 3), signal transduction and activation of transcription 1 and 2	(Hou & Huang 2016, Gholamrezaie *et al.* 2013, Karamoddini *et al.* 2011, Wang *et al.* 2020)
Cinnamomum verum J**.** Presl.	*In vitro* study showed that EO and powder of cinnamon exhibits antiviral activity against NDV in chickens.	Crude and EAPs extracted from bark of *C. verum* showed an increase of the cell growth in PBMCs, indicating immunostimulating effect.	Cinnamaldehyde	Blocking NF-κB activation in immune cells. inhibition of cell viability, proliferation and induction of apoptosis in a dose-dependent manner	(Conti *et al.* 2014, Flechas *et al.* 2018, Flouchi & Fikri-benbrahim 2020, Goyal *et al.* 2018, Roth-Walter *et al.* 2014, Singh *et al.* 2020)
			β-Caryophyllene	Interruption of early steps of the virus life cycle	
			Cinnamyl acetate	NR	
			Cinnamic acid	Down-regulation of TLR-2, HLA-DR, and CD80 and up-regulation of TLR-4 expression by human monocytes	
Eucalyptus globulus Labill.	EO of *Eucalyptus globulus* showed a significant *in vitro* antiviral activity against H1N1	EO has been shown to improve respiratory tract immune function and body immunity with upregulating effect on CD8 cells of Sprague-Dawley rats	1,8-cineole (eucalyptol)	Induction of interferon regulatory factor 3, and up-regulation of NF-κB accompanied by down-regulation of mucin genes (MUC2, MUC19) and modulating of reactive oxygen species	(Astani & Schnitzler 2014, Flouchi & Fikri-benbrahim 2020, Juergens *et al.* 2020, Marchese *et al.* 2017, Salehi *et al.* 2019, Shao *et al.* 2020)
			α-Pinene	NR	
			p-Cymene	Increase of antioxidant enzymes activity, reduction of oxidative stress, modulation of cytokine production by inhibiting NF-κB and MAPK signaling pathways involved in synthesis of pro-inflammatory cytokines	

			Limonene	Inactivation of viral infection through direct Interaction with free virus particles (HSV-1) in a dose-dependent manner	
Mentha pulegium L.	ME showed an important antiviral activity against HSV-1 in HeLa cell line	The powder of aerial part of *M. pulegium* showed a Stimulation of the immune system of broiler chickens by increasing the lymphocytes production and improving the lymphocyte ratio	Pulegone	Inhibition of NF-κB and MAPKs signaling pathways and cytokine production	(Brahmi *et al.* 2017, Choi *et al.* 2018, Mahdavi *et al.* 2013, Parsania *et al.* 2017)
Rosmarinus officinalis L.	EA fraction of *R. officinalis* exerted a strong inhibitory *in vitro* effect against hRSV infection	An *in vitro* study showed a stimulation of adaptive immunity of mice, injected with sheep red blood cells, through oral administration of rosemary leaf extract which increases the number of certain isotypes of antibodies, IgM and IgG, at primary and secondary responses respectively.	Carnosic acid	Suppression of viral gene expression, blocking the expression of hRSV genes; inihibiton of the replication of hRSV	(Ahmed & Babakir-Mina 2020, Lai *et al.* 2009, Li *et al.* 2018, Luo *et al.* 2020, Shin *et al.* 2013)
			Carnosol	Inhibition of Th17 cell differentiation and signal transducer and activator of transcription 3 phosphorylation, and blocking transcription factor NF-κB nuclear translocation	
			Rosmanol	Inhibtion of LPS-stimulated iNOS and COX-2 protein and gene expression, reduction of translocation of the nuclear factor-κB (NF-κB) subunits by prevention of the degradation and phosphorylation of inhibitor κB (IκB)	
			Rosmarinic acid	Inhibition of IFN-γ and IL-4 generation by stimulating $CD4^+$ T cells. Decrease of IFN-γ and IL-4 production *via* activation of T cells and the level of total serum IgE.	
			Eugeniin	NR	

Syzygium aromaticum (L.) Merr. & Perry	AE showed strong anti-HSV-1 activity *in vivo* on brain and skin of mice	Clove EO increased the total white blood cell and enhanced the DTH response in mice (*in vivo*)	Eugenol	Damage to viral envelopes of freshly formed virions and inhibition of initial stage of viral replication	(Cortés-Rojas *et al.* 2014, Carrasco *et al.* 2009, Pramod *et al.* 2010)
Thymus vulgaris L.	EE showed an antiviral activity against NDV, HSV1 and 2, and acyclovir-resistant strains of HSV1 *in vitro* on RC-37 cells	EE showed a potential immunomodulatory role by reducing Pb overload in hepatorenal tissues of Pb-intoxicated rats	Carvacrol	Modulation of pro-inflammatory and anti-inflammatory mediators (IL-17, IFN-γ, TGF-β, IL-6, IL-10, and IL-4), enhancement of autoimmunity by increasing cytokines production	(El-Boshy *et al.* 2019, Flouchi & Fikri-benbrahim 2020, Javed *et al.* 2021, Kuete 2017, Wani *et al.* 2020, Wu *et al.* 2016)
			Caffeic acid	NR	
			Quercetin	Suppression of viral-cell fusion by interaction with influenza hemagglutinin protein	

AE: aqueous extract ; HSV-1 : herpes simplex virus type1 ; EO: essential oil ; DTH : delayed-type hypersensivity ; EE : ethanol extract ; NDV : newcastle disease virus ; Pb : Lead; H1N1 : influenza A virus subtype ; ME: methanolic extract ; EA : ethyl acetate ; hRSV : human respiratory syncytial virus ; IgG : immunoglobulin G ; IgM : immunoglobulin M ; EAPs : ethyl acetate polysaccharides ; PBMCs : peripheral blood mononuclear cells ; NR : No Reported ; NF-κB : nuclear factor kappa ; MAPK : mitogen-activated protein kinase

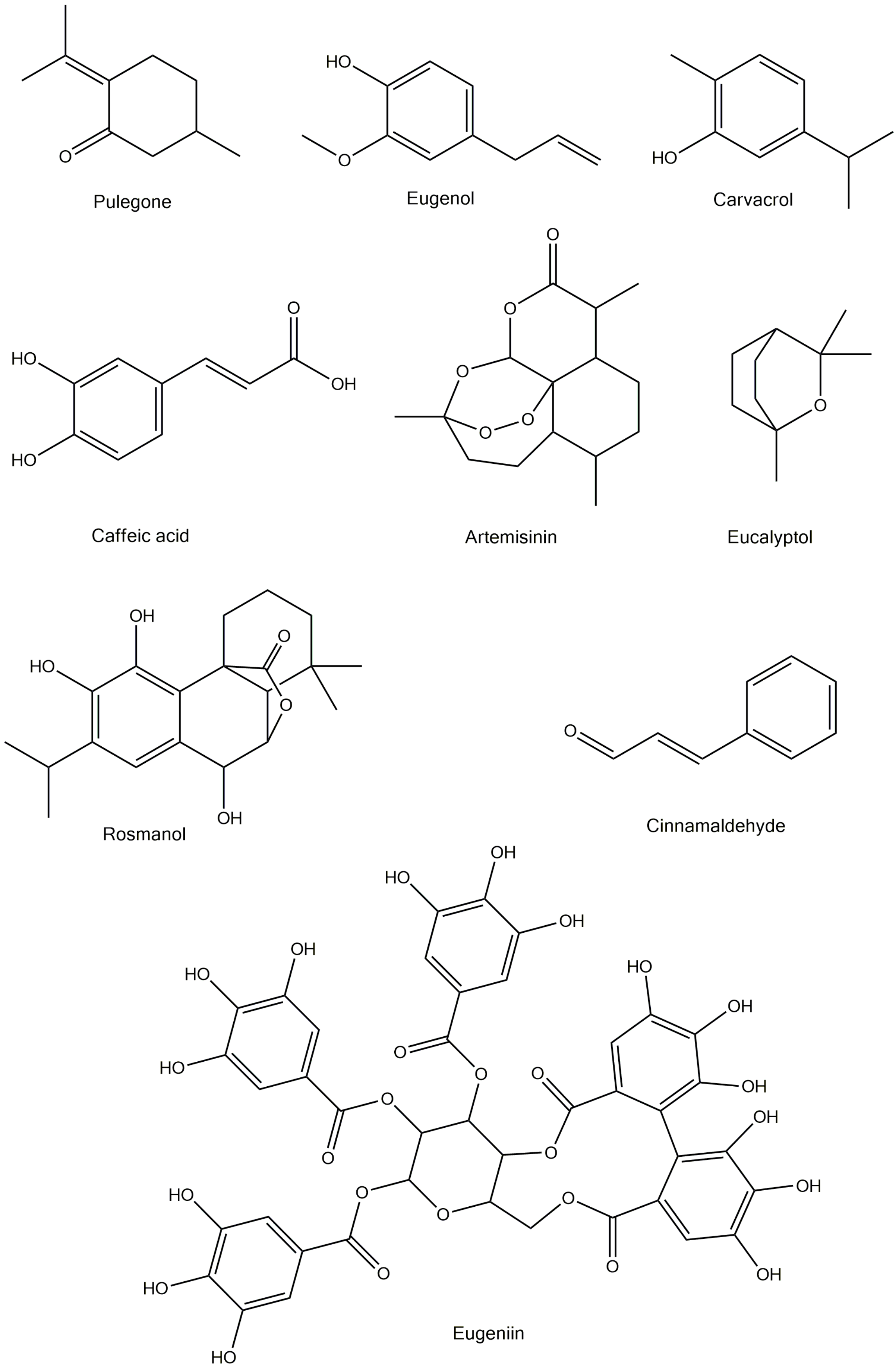

Figure 3. Chemical structures of the main active compounds of the medicinal plants having the highest PUV indices.

Administration routes

In our study, data analysis has revealed that most of the remedy preparations are orally prescribed (43.64%), followed by inhalation (17.27%), massage (5.45%), and cataplasm (0.91%) (Fig.2 (d)). The dominance of the oral administration can be explained by the fact that oral route allows better absorption of active compounds contained in medicinal plants. Our results are consistent with other national and international ethnobotanical surveys reporting that the oral route is the most cited administration mode (Alalwan *et al.* 2019, Chaachouay *et al*. 2019, El Hachlafi *et al*. 2020, Haouari *et al*. 2018).

Conditions of herbal remedies' preparation

In our study area, herbal remedies were mostly prepared from dry (64%) than fresh plant material (16%), and 10% has been prepared from either fresh or dry plants. The use of dry plants can be explained by the fact that drying preserves medicinal plants better and it allows access to different parts of the plant during all seasons of the year (Alalwan et al. 2019). In most cases, the preparation of herbal remedies has been obtained from individual plants with water being the main component. Honey is also used to be mixed with plant powder. Moreover, some preparations are made from plant mixtures such as a juice of Lemon and Ginger (*Zingiber officinale* Roscoe), a fumigation of thyme (*Thymus vulgaris* L.), lavender (*Lavandula angustifolia* Mill.), mugwort (*Artemisia vulgaris* L.), rosemary (*Rosmarinus officinalis* L.) and eucalyptus (*Eucalyptus globulus* Labill.), or infusion preparation from a mixture of thyme, rosemary, mint (*Mentha spicata* L.), and sage (*Salvia officinalis* L.).

Posology

Most herbalists use handle, finger length, and teaspoon as units of measurements. One teaspoon of herbal preparation has been the most common dose used (34 %), followed by a handle (24 %) and finger length (14 %) by a glass of water. Regarding the number of times per day, all herbalists (100 %) recommend using the herbal preparations once a day at night. The duration of treatment was reported until healing (until the disappearance of COVID-19 symptoms).

Satisfaction level of costumers

Most herbalists have reported that their customers were very satisfied (47.36 %). Others were satisfied (34.21 %) with the use of herbal remedies to combat the virus, since they subsequently return to purchase the same herbal recipes to prevent the disease. These high percentages show the potential therapeutic effect of herbal remedies in the treatment of COVID-19. While few clients were unsatisfied (18.42 %) due to the absence of a therapeutic effect that can be explained by an incorrect posology.

Knowledge origin of herbalists

In our survey, most herbalists (82%) acquired their knowledge about the medicinal use of plants from their parents and elderly relatives, whereas 18% built their knowledge by reading books about traditional Arab medicine. This reflects that the relative transmission of herbalism from one to the next generation remains an effective means to transfer this knowledge.

Conclusion

To the best of our knowledge, this survey is the first study carried out in Fez city to focus on the ethnopharmacological knowledge about medicinal plants used by herbalists and traditional healers to combat COVID-19. In short, 49 species, belonging to 28 botanical families, are used in our study area to fight against the pandemic with the domination of the Lamiaceae family. *Syzygium aromaticum* L., *Thymus vulgaris* L., *Eucalyptus globulus* Labill. were the most cited medicinal species. The infusion was the most applied method of herbal preparation and the oral route *has been* the most common route of administration. The ethnobotanical and ethnopharmacological data demonstrated that medicinal plants play a crucial role in the treatment and prevention of COVID-19 since their use is satisfying the inhabitants of Fez city. It also reveals the importance of traditional medicine in the primary healthcare system of Moroccan people, in the study area, as well as the appreciable antiviral properties of the diverse medicinal plants recorded in our study. However, many plants lack ethnomedicinal evidence. Therefore, our ethnobotanical survey could represent baseline data for future biological, pharmacological, toxicological, and phytochemical investigations of the plants listed to identify new, abordable, effective, and ecofriendly antiviral agents. Also, further surveys are needed in other regions of Morocco to collect more data about medicinal species used in the treatment and prevention of COVID-19.

Declarations

List of abbreviations: COVID-19: Coronavirus disease 2019, MAPs: medicinal and aromatic plants, PUV: plant use value, FUV: family use value, 2019-nCoV: 2019 novel coronavirus, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, HSV: virus herpes simplex, HIV: human immunodeficiency, IFV: influenza viruses, EOs: essential oils, SPSS: System Package for Social

Sciences, U: the number of citations per species, N: the number of herbalists interviewed, UVs: the use values of the taxa, ns: total number of species within each family. AE: aqueous extract, DTH: delayed-type hypersensivity, EE: ethanol extract, NDV: newcastle disease virus, Pb: Lead, H1N1: influenza A virus subtype, ME: methanolic extract, EA: ethyl acetate, hRSV: human respiratory syncytial virus, IgG: immunoglobulin G, IgM: immunoglobulin M, EAPs: ethyl acetate polysaccharides, PBMCs: peripheral blood mononuclear cells, PPU: part plant used, L: Leaves, Fl.B: Flower buds, Sp: Spontaneous, D: dry, F: Fresh, Dc: Decoction, If: infusion, OA: oral administration, Im: Imported, Fl: Flowers, Cl: Cultivated, Fm: fumigation, R: root, Pd: powder, AP: aerial part, Rh: rhizome, J: juice, B: Bark, Bu: bulb, Cd: cooked, Fr: fruit, M: maceration, S: seeds, Rw: raw, VO: vegetal oil, St: stigma, Ct: cataplasme, Ma: Massage, Pr: preparation, Ad: administration.

Ethics approval and consent to participate: The data were collected with respect to confidentiality, anonymity and consent. All herbalists were informed about the aim of this study.

Consent for publication: Not applicable.

Availability of data and materials: The data was not deposited in public repositories.

Competing interests: The authors declare no conflict of interest.

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Authors' contributions: Nesrine Benkhaira: Study design, ethnobotany surveys conduction, active participation to methodology structuring, First draft manuscript writing, data analysis and interpretation. Saad Ibnsouda Koraichi: Study supervision, manuscript revision. Kawtar Fikri-Benbrahim: Conception and supervising, contribution to Methodology, manuscript improving and Review-Editing. All authors read, reviewed and approved the manuscript.

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