Ethnobotanical survey on the medicinal usage of two common medicinal plants in Taounate Region: *Artemisia herba-alba* Asso and *Ormenis mixta* (L.) Dumort.

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Research

Abstract

Background: This study aims to valorize two predominant medicinal plants commonly used in Taounate Region to treat and prevent many diseases, namely *Artemisia herba-alba* Asso (*A. herba-alba*) and *Ormenis mixta* (L.) Dumort (*O. mixta*). The objective of this study is to carry out a series of ethnobotanical surveys to collect information on the traditional use of these plants by the local population.

Methods: An ethnobotanical survey was conducted in Taounate Region, in a period of four months (from March to June 2020). Semi-structured interviews were conducted with 150 individuals from the population. A statistical analysis of the collected data was performed using SPSS (System Package for Social Sciences, version 21) and Microsoft Office "Excel 2016". The bibliometric research was carried out using international databases to confirm the ethnomedicinal practice of the surveyed medicinal plants.

Results: In short, data revealed that leaves and stems are the most used plant parts for *A. herba-alba*. As for *O. mixta*, flowers are the most recommended to prepare natural remedies. Decoction was the most used preparation method, and oral route is the most common administration method for both plants. The two medicinal plants are involved in the treatment of digestive, genitourinary, metabolic, neurological, respiratory, and osteo-articular diseases. No side effects were reported due to the use of *O. mixta,* whereas *A. herba-alba* can cause ulcers or allergies when used at a high dose.

Conclusions: Information collected in our ethnobotanical study and data obtained from literature searching could provide basic data for future investigations on *O. mixta* and *A. herba-alba*. Thus, their ethnomedicinal use needs in-depth phytochemical, pharmacological, toxicological, and clinical research to clarify their effectiveness and safety.

Keywords: medicinal plants, *Ormenis mixta*, *Artemisia herba-alba*, Taounate, Morocco, ethnobotanical.

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Background

Man has long used medicinal and aromatic plants from his environment to treat and prevent all kinds of diseases (Lampert 2019). In Africa, more than 80% of the populations have recourse to traditional pharmacopoeia to deal with health problems, especially Moroccan populations which still depend on herbal medicinal usage thanks to the ecological and floristic diversity of Morocco (Benkhaira *et al.* 2021, Bourhia *et al.* 2019, Msanda *et al.* 2021, Tugume & Nyakoojo 2019).
Indeed, numerous scientific research exposed the richness of medicinal plants in bioactive compounds that are responsible for their benefits and biological properties (El Hachlafi *et al.* 2020, Kumar *et al.* 2021), hence their extensive use in many fields: culinary (spices, dyes) (Stefanaki & Tinde 2021), agricultural (herbicides) (Máthé *et al.* 2015), and medical fields (herbal medicines) (Shahid *et al.* 2013). Thus, herbal remedies deserve to be scientifically valid.

Notably, ethnobotanical knowledge provides a starting point for many successful drug screening projects in recent years, and it has been a fundamental source for the discovery of drugs, therefore, our study aims to document adequately the traditional practices of two medicinal plants from the population of Taounate Region which have a long association with herbs (Faruque *et al.* 2018).

Taounate is a town in northern Morocco, situated on the southern slopes of the Rif Mountains. The town had 37.616 inhabitants and covers an area of 5616 km^2 but rich in plant diversity (Bouarfa *et al.* 2020). Taounate is known by the abundance of two medicinal plants namely *Artemisia herba-alba* Asso and *Ormenis mixta* (L.) Dumort. Both belonging to the Asteraceae family; however, few studies have been found in Morocco about the phytochemical or pharmacological properties of these plants.

Artemisia herba-alba Asso (syn. *Artemisia maritima* L., *Artemisia brevifolia* Wall.) known also as desert wormwood (known in Arabic as "shih," and French as "armoise blanche"), is widely distributed in North Africa (Nigam *et al.* 2019). Over the past decade *Artemisia* species have been used traditionally by different populations (Mohamed et al. 2010). In Moroccan folk medicine, the plant is used to treat arterial hypertension and/or diabetes. Herbal tea from this species has been used as analgesic, antibacterial, antispasmodic, and hemostatic agents. This plant is also considerable as a fodder for sheep and for livestock in Algeria where it grows abundantly (Nigam *et al.* 2019).
Ormenis mixta (L.) Dumort having as synonyms: *Cladanthus mixtus* (L.), *Chamaemelum mixtum* (L.) (The Plant List 2021), is an endemic aromatic plant distributed mainly between septentrional Western Morocco, and the septentrional part of central Morocco. The plant essential oil (EO) finds also traditional uses and it is a general tonic, neurotonic, aphrodisiac, endowed with anti-infectious, bactericidal and parasiticidal properties (Anass *et al.* 2015).
Since ethnomedicinal knowledge is transmitted verbally from one generation to the next, our main objective is to comprehensively document the ethnomedicinal information of the population of the Taounate region on *A. herba-alb*a and *O. mixta*, in to build a database of these medicinal plants and their traditional uses. We have also documented from the literature, ethnomedicinal use in other regions, the phytochemical composition, and biological properties of these two medicinal plants.

Materials and Methods

Study area

Taounate is a town in the Rif Mountains region of northern Morocco. It is located in the Fez-Meknes region at around 34°32'9"N 4°38'24"W. The town had 37.616 inhabitants as of the 2014 Moroccan census. Its total area is 5616 km^2. It is composed of 44 rural municipalities and 5 urban communes (Figure 1) (Wikipédia 2021).

Geographically, the territory of Taounate is constituted overall by two distinct parts: the northern and southern parts. A Northern part having mountainous terrain attached to the Rifain domain, constitutes about 40% of its area. The maximum altitudes peak from the East to the West, 1730 m (Jbel Tajerfet), 820 m approximately (Jbel Al-Bibane). The minimum requirements follow in the same direction the bed of Oued Ourgha and vary from 300 to 800 m. A southern part with hilly and hectic relief, attached to the pre-rifain area, and which constitutes about 60% of the total area. The altitudes are relatively mitigated and vary from 150 m (Wadi Innaouen) to 1000 m at Jbel Zeddour (Bouarfa *et al.* 2020).

In terms of climate, Taounate is covered by three bioclimatic strata which promote the development and diversity of its flora. The climate is typically Mediterranean and characterized by the alternation of two seasons, winter, and summer. The average rainfall is around 790 mm with maximums which can be around 2.000 mm at Jbel Outka. The average temperature is about 16.9 °C (with a maximum of 45 °C and a minimium of 2 °C) (Hafsé *et al.* 2015).

The economy of Taounate is mainly articulated around agriculture (grain farming, fig trees), particularly the cannabis culture, which threatens the region both ecologically and socially (Bouarfa *et al.* 2020).

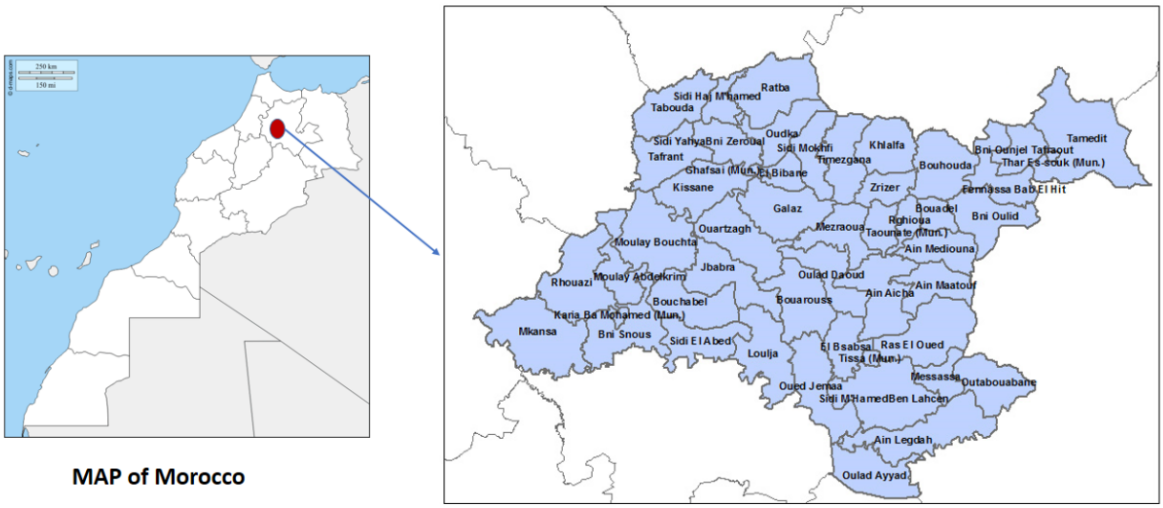

Figure 1. Location of the study area; Taounate-Morocco.

Ethnobotanical survey

The ethnobotanical survey lasted over a period of four months, from March to June 2020. The data were collected through semi structured interviews. The Arabic language was used to collect data and plant names were mainly given in Tashelhit (Berber dialect). A total of 150 people were individually interviewed for this purpose. The time devoted to each interviewer varies between 10 and 40 min.

The data collected are related to the informant (age, gender, level of education, family situation and socioeconomic level) and to the medicinal plants (vernacular name, plant type, harvest time, part used, posology, preparation method, diseases treated, diagnosis and side effects).

Data analysis

The data collected have been statistically analyzed using SPSS (System Package for Social Sciences, version 21) and Microsoft Office "Excel 2016". Socio-demographic and ethnobotanical data have been analyzed by a simple descriptive statistical method using percentages and frequencies.

Literature background

In order to ensure the ethnomedicinal practice of *A. herba-alba* and *O. mixta*, bibliometric research has been performed about the pharmacological and biological properties of the surveyed medicinal species. Data has been collected from Pubmed, Scopus, Web of Science, Medline, Sciencedirect, Springerlink and Google Scholar. The following Keywords were used to facilitate the collection of data: "*Artemisia herba-alba"* or "*Artemisia maritima",* "*Ormenis mixta"* or "*Cladanthus mixtus",* ethnobotanical, and ethnopharmacological, and phytochemical, and essential oil, and pharmacological." ChemDraw Ultra 12.0 Software was used to draw the chemical structures. IUPAC names of the reported chemical compounds were cheeked using PubChem databases.

Results and Discussion

Socio-demographic profile

In the study area, most respondents belong to the age group of 40-60 years (65.33%), followed by those who were between 20 and 40 years (24%), while the oldest over sixty were less numerous (8.66%), and respondents with an age less than 20 came in last position (2%) (Table 1). Interviews show that older people possess a much greater knowledge of plants than younger people. This may be justified by the fact that elderly people hold most of the ancestral knowledge that is part of oral tradition. Similar findings were observed in previous ethnobotanical studies made in other regions in Morocco (Barkaoui *et al.* 2017, Chaachouay *et al.* 2019, Kachmar *et al.* 2021).

The high proportion of participants was dominated by women, with 62% followed by men with 38%. These data show that women were more connected to traditional practices than men. This is due to the fact that women were frequently sitting at home and are responsible for caring for their children and maintaining their families' health in the most efficient and economical way possible. These findings are consistent with other ethnobotanical work at national scale (Barkaoui *et al.* 2017, Bencheikh *et al.* 2021, Chaachouay *et al.* 2019).

Regarding the educational level, data showed that 65% of the respondents were illiterate, followed by those having a secondary and primary level, 21% and 10% respectively. However, people with a university-level education represented a low percentage of 4 %. The use of medicinal plants decreases as the education level increases. Our findings resonate with other results in which knowledge on the use of medicinal plants is owned by the illiterate (Bencheikh *et al.* 2021).

In our study, 63% of the interviewees had a moderate socio-economic level and 36% a low level, while no informant had a high level. This is due to the high cost of modern medical treatments. These results are like those obtained by Jeddi *et al.* (2021).

Data showed that the medicinal plants are much more used by married (65%) than by single people (35%). This could be explained by the fact that families with average or low incomes can minimize or avoid the high costs required by doctors and pharmacists. These findings coincide with those of Jeddi *et al.* (2021).

Table 1. Socio-demographic characteristics of informants interviewed.

Variable	**Subgroup**	**Number**	**Percentage (%)**
Gender	Male	57	38
	Female	93	62
Age	>20	3	2
	{20-40}	36	24
	{40-60}	98	65.33
	>60	13	8.66
Educational level	Illiterate	97	65
	Primary	15	10
	Secondary	31	21
	University	7	4
Marital status	Married	97	65
	Single	53	35
Socio-economic status	Highest	0	0
	Medium	94	63
	Lowest	56	37

Artemisia herba-alba

Denomination, type of plant, technique and time of harvest

In the study area, most respondents reported the vernacular name of the plant species in Tashlhit, 'Ifsi', while the city dwellers mentioned three different nominations in Arabic language: 'Chih, elkayssoum, chih elkarssani'. All respondents (100%) indicated that the plant is spontaneous and harvested manually in the spring season.

Plant parts used

In general, the aerial part (AP) has been reported as the most used part of *A. herba-alba* (55%), followed by leaves (30%), stems (7%), flowers (5%), and roots (3%) (Figure 2). This observation agrees with another ethnobotanical study which indicate that the AP of *A. herba-alba* is the most used in the Northeastern Part of Morocco (Kachmar *et al.* 2021). The frequent use of the AP and leaves could be explained by the ease of harvest and simplicity of the herbal remedy preparation. Likewise, leaves are the site of photosynthesis and reservoirs of secondary metabolites that are responsible for benefits and biological properties of the plant species (Bencheikh *et al.* 2021, Benkhaira *et al.* 2021).

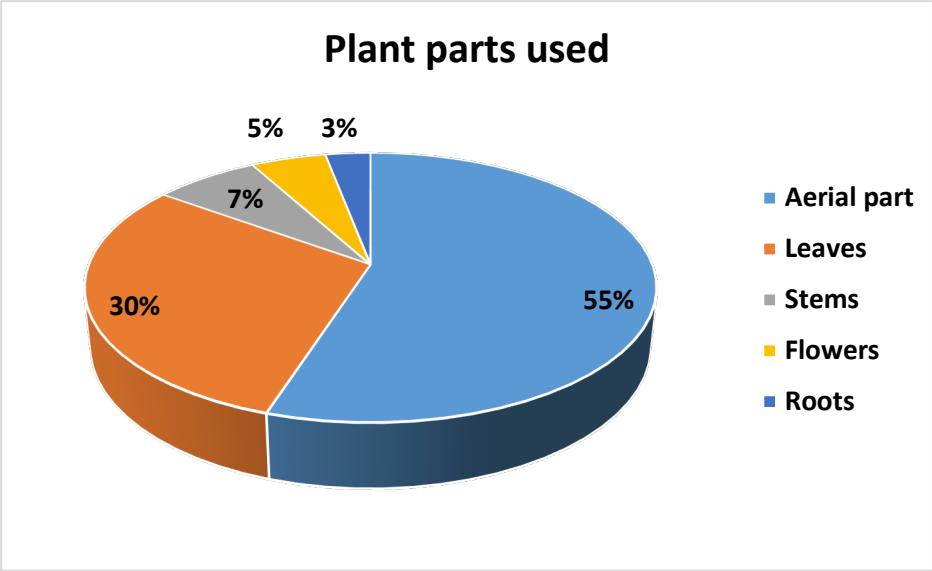

Figure 2. Percentage of the different plant parts used.

Posology

According to the population surveyed, *A. herba-alba* is used in the form of extracts (88%) and EO (12%). All respondents mentioned that they use dry plant material.

Our study showed that decoction was the dominant preparation method with a percentage of 57% followed by infusion and poultice with respective percentages of 31 and 12 %. Decoction is an extraction method by boiling plant material to dissolve the chemicals of the material (Bozyel *et al.* 2020). While infusion method extracts the chemicals from the plant material by soaking it in cold or boiling water for a short time (Swami *et al.* 2008).

Other ethnobotanical studies cited that decoction is the most used preparation method of *A. herba-alba* (Eddouks *et al.* 2002, Kachmar *et al.* 2021). Decoction method is widely used because it allows collecting the maximum of bioactive molecules and attenuates specific recipes' toxic effects. It also prevents the destruction of certain ingredients (Bencheikh *et al.* 2021, El Hachlafi *et al.* 2020).

The decoction method was described by some interviewees. They recommended mixing two spoons of powder from the aerial part or chopped dry leaves with a glass of cold water (200-250 mL) for one night, under cover. Then, the covered mixture is brought to a boil for 20 minutes. After allowing it to cool, the mixture is filtered through a sieve.

Our study revealed that the oral administration is the most recommended by the population (78%), followed by dermal route (massage) (22%). The study realized by Kachmar *et al.* confirms our results; showing that *A. herba-alba* is mainly taken orally in north-eastern Morocco. The oral route is an abundant administration method because it allows a better absorption of the active compounds contained in the plant (Benkhaira *et al.* 2021, El Hachlafi *et al.* 2021).

Diseases treated by *A. herba-alba*

Our ethnobotanical study revealed that *A. herba-alba* is consumed mainly for the treatment of digestive and neurological disorders (100% each). It is also used to treat genitourinary (70%), metabolic diseases (52%), osteo-articular (3.5%), dermatological (4%) and respiratory diseases (3%). Kachmar *et al.* revealed in their work that *A. herba-alba* is used in northeastern Morocco to manage the gastrointestinal infections, abdominal pain, cold, and nausea. Other study performed by Belhaj *et al.* mentioned that the plant is highly recommended to fight against diabetes in the High Atlas Central of Morocco. In Daraa-Tafilalet region (Province of Errachidia), the plant is consumed to prevent gastrointestinal disorders, diabetes, ulcer, fever, Intestinal parasites, rheumatism, constipation, heart diseases, menstruation pains, cough, liver diseases, skin diseases, kidney diseases, cancer, hair loss and anemia (Eddouks *et al.* 2002). In oriental Morocco region, people use the plant to relieve pathologies of the digestive system and manage diabetes and dermo-cosmotological disorders (Jamila & Mostafa 2014). The literature has revealed other ethnomedicinal uses of *A. herba-alba* in Morocco. Indeed, this plant can obviously treat wounds and

rheumatism, stimulate appetite, facilitates digestion, removes bad breath, and manage emmenagogue, nausea, diarrhea, and stomach pain (Idm'hand *et al.* 2020).

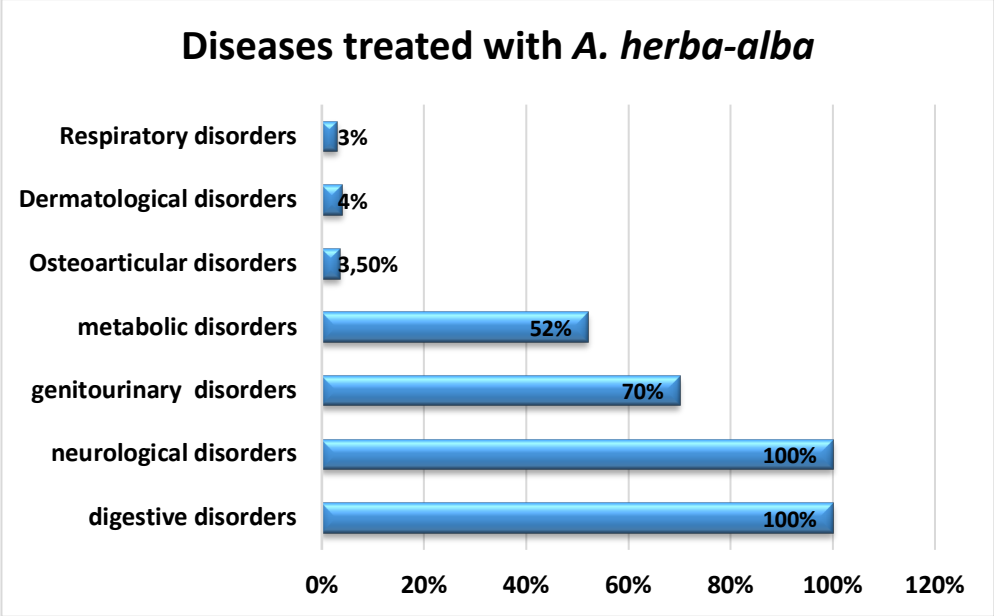

Figure 3. Percentage of the different diseases treated by *A. herba-alba.*

Literature review on bioactivities of *A. herba-alba*

Many of traditional medicinal uses of *A. herba-alba* have been tested by scientists. Several works have reported some pharmacological properties of this plant, including antimicrobial, antidiabetic, insecticidal, antiinflammatory, antinociceptive, antioxidant, and anticancer (Moufid & Eddouks 2012). The table 2 presents a brief overview of some recent studies about main pharmacological, biological, and phytochemical properties of *A. herba-alba*. The structures of the principal chemical compounds reported in the extracts of these plants are drawn in Figure 4.

Several investigations have demonstrated that *A. herba-alba*, especially its EO, possesses various biological and pharmacological properties, including antibacterial, antioxidant, antifungal, neuroprotective, anticancer, antidiabetic, antinociceptive, insecticidal and anti-inflammatory effects (Amor *et al.* 2019, Ed-Dra *et al.* 2021, Eljazi *et al.* 2020, Khlifi *et al.* 2013, Qnais *et al.* 2016, Sekiou *et al.* 2021, Younsi *et al.* 2016).

The antibacterial activity of *A. herba-alba* was clearly elucidated in the literature against a plethora of bacterial strains, including both gram-positive and gram-negative bacteria. The study of Ed-Dra *et al.* (2021) showed that *A. herba-alba* EO has a strong antibacterial effect against numerous bacteria such as *E. coli, S. aureus, Salmonella typhimurium, Enterococcus faecalis, Klebsiella pneumonia,* and *P. aeruginosa* with an inhibition zone diameter ranging from 9 to 17 mm and MIC from 0.156 ± 0.00 to 5.0 ± 0.00 mg/mL. The same species was studied by Mighri *et al.* (2010) who found that the disc diffusion method (DDM) recorded an important inhibitory zone (IZ) varying from 10.0 ± 0.0 to 22.7±1.2 mm (Mighri *et al.* 2010).

Furthermore, Bertella *et al.* (2018) have evaluated the antibacterial activity of an Algerian *A. herba-alba* EO against 15 strains isolated from in-patients, including 3 strains of *Methicillin-resistant Staphylococcus aureus*, 5 strains of extended spectrum β-lactamase producing bacteria (*E. coli* (ESBL ECB1 and ESBL ECB2), *K. pneunomoniae* (ESBL KPB1 and ESBL KPB2) and *Proteus mirabilis* (ESBL PMB1)), and 7 strains of sensitive bacteria (*Staphylococcus epidermidis, Staphylococcus haemolyticus* (SHB1), 2 *Acinetobacter baumannii* (ABB1 and ABB2), *Proteus mirabilis* (PMB2), *Salmonella enteritidis* (SEntB1) and *Klebsiella oxytoca* (KOB1)). The results showed that *A. herba-alba* EO exhibits remarkable antibacterial effect against the studied strains, especially against gram-positive bacteria with MIC values ranging from 5 to 10 mg/mL (Bertella *et al.* 2018).

Additionally, the antifungal properties of *A. herba-alba* was also investigated against an important number of fungal and yeast isolates. Recently, Ed-Dra *et al.* (2021) have tested *A. herba-alba* EO against human pathogenic yeast isolated from patients suffering from condidosis including *Candida albicans, C. glabrata, C. sake,* and *C. tropicalis*. They found that *A. herba-alba* EO has a promising anticandidal activity against the studied yeast (IZ ranging from

10.7± 0.6 and 22.3± 0.6 mm). Moreover, it has been reported that *A. herba-alba* E.O ensures a great antifungal effect against *Aspergillus niger* (IZ= 23.6 ± 1.5mm) (Amor *et al.* 2019).

The wide ethnomedicinal use of *A. herba-alba* encouraged numerous research teams to evaluate the antioxidant potential of this plant species. Indeed, through different *in vitro* antioxidant assays, such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), β-carotene bleaching, ferric chelating ability, and ferric-reducing power. Younsi *et al.* (2016) found that EO and methanolic extract of *A. herba-alba* exhibit a considerable antioxidant capacity ($IC_{50\ (DPPH)}$ =100 - 5030 µg/mL, $IC_{50\ (\beta\text{-carotene})}$=524 - 1590 µg/mL, $IC_{50\ (ferric\ chelating)}$=1720 - 2300 µg/mL, and IC_{50}=372 - 79 µmol Fe^{2+}/g). This effect was mainly attributed to the abundance of phenolic compounds contained in *A. herba-alba* extracts.

More recently, Bouchara *et al.* (2021) assessed the anti-inflammatory effect of different extracts of *A. herba-alba* collected in East of Algeria (water, methanol/water (80:20, v/v), ethanol/water (80:20, v/v), acetone/water (80:20, v/v) and a mixture of methanol, ethanol, acetone, and water (25:25:25:25, v/v/v/v) using maceration and the Microwave assisted extraction. The anti-inflammatory properties of the plant were tested via different methods, quantification of reactive oxygen species (ROS) production and Enzymatic activities measurements (Glutathione reductase (GR), Glutathione peroxidase (GPx), and Glutathione S-transferase (GST) activities), and determination of Total glutathione and total protein thiols. According to data obtained, *A. herba-alba* extracts could reduce and block ROS production at high doses in living cells. Indeed, the methanol macerated *A. herba-alba* extracts elevated GSH levels at different concentrations in Jurkat cells. This effect is correlated with GR activity, and reinforce the reduced glutathione, with concomitant increases of GST, GPx, and free protein thiols levels. In addition, acetone macerated extracts enhanced GSH levels and GR activity, accompanied by an increase of GST, GPx, and free thiol protein expression levels, in a dose-dependent manner. These results submit beneficial properties of *A. herba-alba* consumption in preventing inflammatory disorders (Bouchara *et al.* 2021).

As to anti-cancer activity, an interesting investigation was carried out on the effect of Egyptian *A. herba-alba* extract on the proliferation of solid tumor cells in Ehrlich Solid Carcinoma bearing mice. The study showed that the oral administration of *A. herba-alba* extract (300 mg/kg), daily for five to ten consecutive days, could induce a significant reduction in tumor size, tumor weight and mice body weight, as well important rise in apoptotic deoxyribonucleic acid (DNA) damage induction in a time-dependent manner. The *A. herba-alba* extract also increased the expression level of tumor protein 53 (tp53) gene and minimized the expression of Kirsten rat sarcoma virus (K-ras) in a time-dependent manner. Also, slight histological lesions were detected in the liver and kidney tissues of mice treated by *A. herba-alba* extract compared with the large histological lesions noticed in the same tissues of artesunate and cisplatin treated groups. Thus, *A. herba-alba* extract could exhibit promising potential antitumor efficacy with greater safety (Mohamed *et al.* 2020).

Phytochemistry of *A. herba-alba*

According to the literature, the phytochemistry of essential oils extracted from different parts of the plant *A. herba-alba* has been more studied than the crude extracts. Indeed, Bouchara *et al.* (2021) investigated the quantitative chemical analysis according to the Folin-Ciocalteu assay of dried samples that were macerated or subjected to microwave-assisted extraction in various solvents (water, acetone, methanol, ethanol, or a mix of all solvents at equal volumes). Results showed that higher quantities of total phenolic compound (TPC) were obtained using the microwave method. In maceration mode, acetone extract contained the highest proportion of TPC followed by methanol, and ethanol extracts, 150.42 ± 0.43, 140.09 ± 0.010, 139.31 ± 0.010 mg GAE/g dry weight, respectively. In microwave-based extraction, acetone, methanol, and ethanol provided similar amounts of TPC ranging from 167.47 ± 0.005 to 177.32 ± 0.007 mg GAE/g dry weight. Noteworthy, water in both extraction methods yielded lower TPC compared to organic solvents. Also, the combination of solvents did not enhance polyphenols extraction in both methods.

Regarding the qualitative analysis, Amor *et al.* (2019) showed that oxygenated monoterpenes predominated in *A. herba-alba* EO extracted by hydrodistillation and collected from Azzemour region, Southwest Morocco. The gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) analysis showed that *cis*- and *trans*-thujone, Vanillyl alcohol and *nor*-davanone are the principal constituents. These results agree with the work of Aghaei & Sharifian 2011 where *cis*- and/or *trans*-thujone are the main constituents of the plant EO extracted by hydrodistillation and collected from Iran. While the EO extracted from *A. herba-alba* in Er-rachidia province, South-central Morocco, was characterized by chrysanthenone and camphor as main constituents (El Ouahdani *et al.* 2021).

Table 2. Pharmacological and biological activities of *A. herba-alba*.

Activity	PU	Extract	Study type	Method	Key Results	Chemical compound	References
Antibacterial	AP	EO	*In vitro*	DDM BDM against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Enterococcus faecalis*, *Klebsiella pneumonia, Pseudomonas aeruginosa*	IZ= 9-17 mm MIC= (0.156 ± 0.00 - 5.0 ± 0.00) mg/mL MBC= (0.156 ± 0.00- 10.0 ± 0.00) mg/mL	Davanone	(Ed-Dra *et al.* 2021)
Antifungal	AP	EO	*In vitro*	DDM *against Aspergillus niger*	*IZ=23.6 ± 1.5mm*	α-thujone, β-thujone and vanillyl alcohol	(Amor *et al.* 2019)
insecticidal	AP	EO	*In vitro*	fumigant bioassay against *Tribolium castaneum*	LC_{50}= 42.15% and 59.8% after 30 and 60 days of storage, respectively	β-thujone, 1,8-Cineole, Camphor, α-thujone	(Eljazi *et al.* 2020)
Anti-inflammatory	AP	EO	*In vivo*	Sub-cutaneous air-pouch model in rats	inhibition of the inflammatory process by reducing cell migration & inflammatory mediators (IL-6, TNF, PGE2, and NO) produced in the pouch	(E)- caryophyllene	(Qnais *et al.* 2016)
Antinociceptive	AP	EO	*In vivo*	intraperitoneal injection of acetic acid and thermal (hot-plate) nociceptive tests in rats (visualized as abdominal writhing)	An increase in the latency response in the hot-plate test with ED_{50} of 85.3±4.1 mg/kg	(E)- caryophyllene	(Qnais *et al.* 2016)
Anticancer	L	ME	*In vitro*	MTT assay against human bladder carcinoma RT112, human laryngeal carcinoma Hep2 and human myelogenous leukemia K562	IC50 = (59.05 ± 3.68 - 90.96) mg/L	NI	(Khlifi *et al.* 2013)
Anthelmentic	F and AP	ME	*In vitro*	Adult Motility and Egg Hatch Inhibition assays against *Haemonchus contortus*	The flower's ME induced a significant egg hatching with an inhibition of 98.67%	NI	(Ahmed *et al.* 2020)
Nephro-protective	Fresh AP	AE	*In vivo*	Induction of experimental diabetes by alloxane	Improvement of GSH level, regulation of glucose homeostasis, reduction in urinary volume, serum creatinine, and urea	NI	(Sekiou *et al.* 2021)
Antioxidant	AP	ME - EO	*In vitro*	DPPH, β-carotene bleaching, ferric chelating ability, ferric-reducing power	IC_{50}=100 - 5030 µg/mL IC_{50}=524 - 1590 µg/mL IC_{50}=1720 - 2300 µg/mL IC_{50}=372 - 79 µmol Fe2+/g	glycosyl flavonoids and phenolic acids, mainly caffeoylquinic acid α-Pinene, Camphene, Sabinene, β-Pinene, p-Cymene	(Younsi *et al.* 2016)

PU: Part used; EO: essential oil; AP: aerial part ; DDM: disc diffusion method; BDM: broth dilution method ; IZ: inhibitory zone ; MIC: minimal inhibitory concentration ; MBC: minimal bactericidal concentration ; LC_{50}: Lethal Concentration 50; IL-6: interleukine-6; TNF: tumor necrosis factor; PGE2: *Prostaglandin E2;* NO: Nitric Oxide; ED_{50}: Effective dose 50; L: leaves ; ME: Methanolic extract; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NI: not-identified; F: flowers ; AE: Aqueous extract ; GSH: glutathione ; DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate.

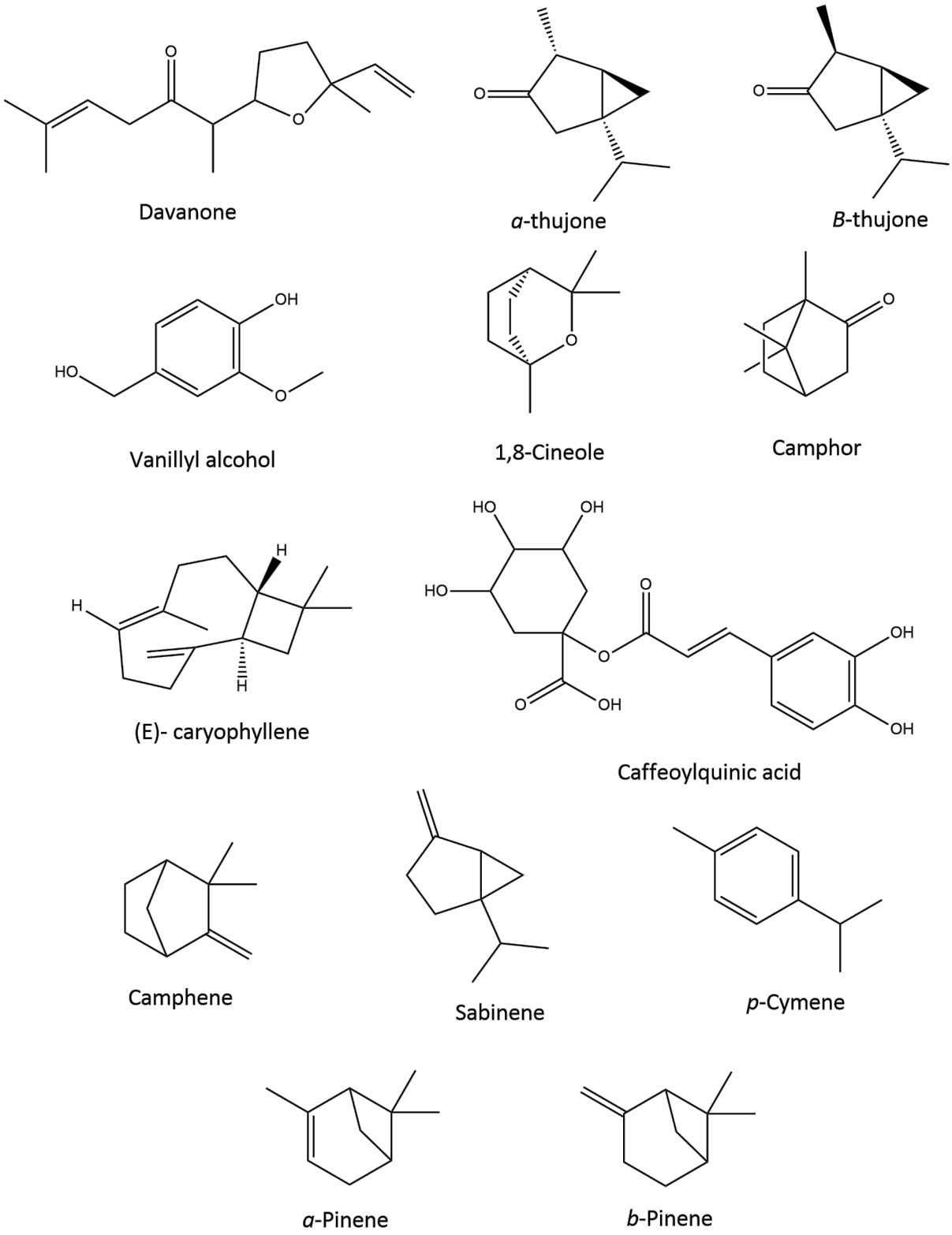

Figure 4. Chemical structures of some volatile compounds of *A. herba-alba* EO.

Moreover, an interesting study diagnoses the qualitative components of *A. herba-alba* volatile oil from Iraq by cold and hot aqueous solvent. GC-mass, Thin-layer chromatography (TLC) showed that EO extracted by cold aqueous dissolvable contains mainly Camphor, Filifolide A, 1-ethynyl-4-methoxy-4-methyl-2-cyclobuten-1-ol, Lineatin, 2-pentanoylfuran, davana ether, caryophyllene oxide, beta-Myrcene, vulgarin, trans-caryophyllene, (2-Ethylhexyl), and bis-phthalate. While the volatile oil from the hot aqueous solvent covers 2-methyl-4-nitroresorcinol, cis-hydroxydavanone, vulgarin, and dihydroxanthin as major contituents (Al-any *et al.* 2019). Besides, Ed-Dra *et al.*

(2021) indicated through the Gas Chromatography-Flame Ionisation Detector (GF-FID) and GC-MS that *A. herba-alba* EO from the East Morocco contain davanone, Davana, Ether Isomer 1 and 2, 1,2 Dehydro-3-hydroxyisodavanone, and Camphor as main components.

More interestingly, Tilaoui *et al.* (2015) compared the chemical composition from capitulum, leaves, aerial part, and stems of *A. herba-alba* harvested in central Eastern region of Morocco. The chemical composition of EOs was studied using GC-MS analysis. It showed that leaves EO includes mainly oxygenated sesquiterpenes, sesquiterpenes and esters. The leaves EO is characterized by Eucalyptol (1,8-Cineole), 2,5-Octadecadiynoic acid, methyl ester, α-bulnesene, and Bisabolone oxide. In stems EO, esters constitute the major fraction, and the major components are acetic acid, butyl ester, Ethyl linoleate, 3,16-Octadecadiynoic acid, and methyl ester. While capitulum EO is relatively rich in oxygenated and monocyclic monoterpenes. The most abundant compounds in the capitulum part are β-Guaiene and Bisabolone oxide. On the other side, the aerial part EO (capitulum and leaves) is marked by a wealth of oxygenated sesquiterpenes and pinane skeleton, other constituents are representative by monoterpene skeleton with thujane, monoterpenes with bornane skeleton and monocyclic monoterpenes. Bisabolone oxide, Farnesene epoxide E, and verbenol are the major chemical constituents of the aerial part EO. These data shows that the chemical composition variability of EOs depends on the nature of botanical parts of *A. herba-alba* (Tilaoui *et al.* 2015).

Ormenis mixta

Denomination, type of plant, technique and time of harvest

In the study area, most respondents reported that the vernacular name of the plant species is Hellâla. All respondents (100%) indicated that the plant is spontaneous and harvested manually in the spring season.

Plant parts used

The most used parts of *O. mixta* in Taounate Region were found to be flowers with a rate of 62.50%, followed by the whole plant (25%), leaves (10%), stems (2%), and rhizomes (0.50%) (Figure 5). The ethnobotanical study of El Hachlafi *et al.* also mentioned that flowers of *O. mixta* are widely used to treat metabolic diseases in Rabat-Sale-Kenitra region. Another Ethnobotanical survey showed that the whole plant of *O. mixta* is frequently used by the population of Agadir to treat diabetes (Ouhaddou *et al.* 2020). Many studies demonstrated that flowers own valuable therapeutic effects since they include several bioactive molecules (Gunawardana & Jayasuriya 2019).

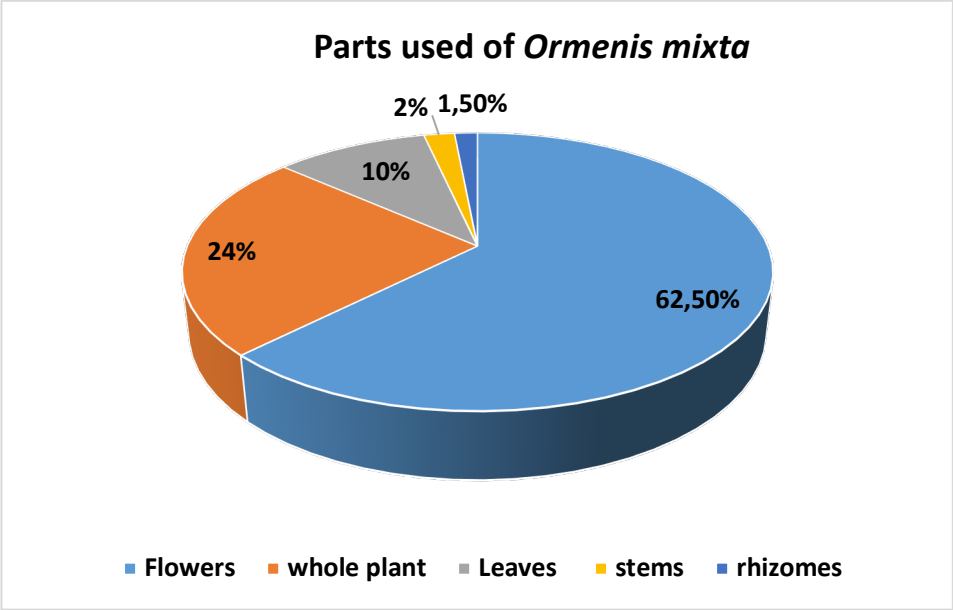

Figure 5. Percentage of the different parts used of *O. mixta* for remedies preparation.

Posology

According to the population surveyed, *O. mixta* is also used in a dry state, and prepared in three forms: herbal tea (52%), EO (27%), and extracts (21%). These results confirm the findings of an ethnobotanical study carried out in the Gharb plain of Morocco (Bouhlal *et al.* 2017). Our study revealed that the decoction method is the most recommended for the preparation of *O. mixta* (75%), followed by infusion (18%), then other methods such as

powder, cataplasm, and maceration (7%). According to the explanations of some individuals from the Taounate Region, the decoction method allows an increase of the body temperature which boosts the immune response. Furthermore, the decoction is frequently used because it allows a best collecting of the active ingredient of medicinal plants. The preparation method of *O. mixta* decoction is the same as that described for *A. herba-alba*. Data showed that the remedy preparations of *O. mixta* are mainly prescribed orally (85%), followed by dermal application (15%).

Diseases treated by *O. mixta*

The present work revealed that *O. mixta* is mainly involved in the treatment of neurological diseases, with a rate of 97%, and digestive diseases (92%), followed by dermatological diseases (50%) then urogenital diseases (30%). The other diseases, namely respiratory, metabolic and osteo-articular diseases, are the least mentioned with a rate of 7% (Figure 6).

It was declared in the literature that *O. mixta* extracts are used in Moroccan traditional medicine as an anxiolytic and to rebalance the central nervous system. The *O. mixta* essential oil is also exploited as natural antimicrobial, anti-inflammatory, and antioxidant agents (El Mihyaoui *et al.* 2021). It was also mentioned that *O. mixta* is used by the population of Sidi-Boughaba (Mahdia, Morocco) to treat stomachic, anthelmintic, antidiabetic, anxiolytic, nervous breakdown, hepatic and gastric insufficiencies (Merghoub *et al.* 2009). Another ethnomedicinal survey performed by Zeggwagh *et al.* in Fez, Morocco, showed that this plant is recommended to tend to Digestive and Neurological troubles. In addition, El Hachlafi *et al.* reported that *O. mixta* is involved in the treatment of diabetes and arterial hypertension in Rabat-Sale-Kenitra region. Furthermore, Bouhlal *et al.* indicated that *O. mixta* is recommended to treat digestive diseases, headaches, and microbial infections.

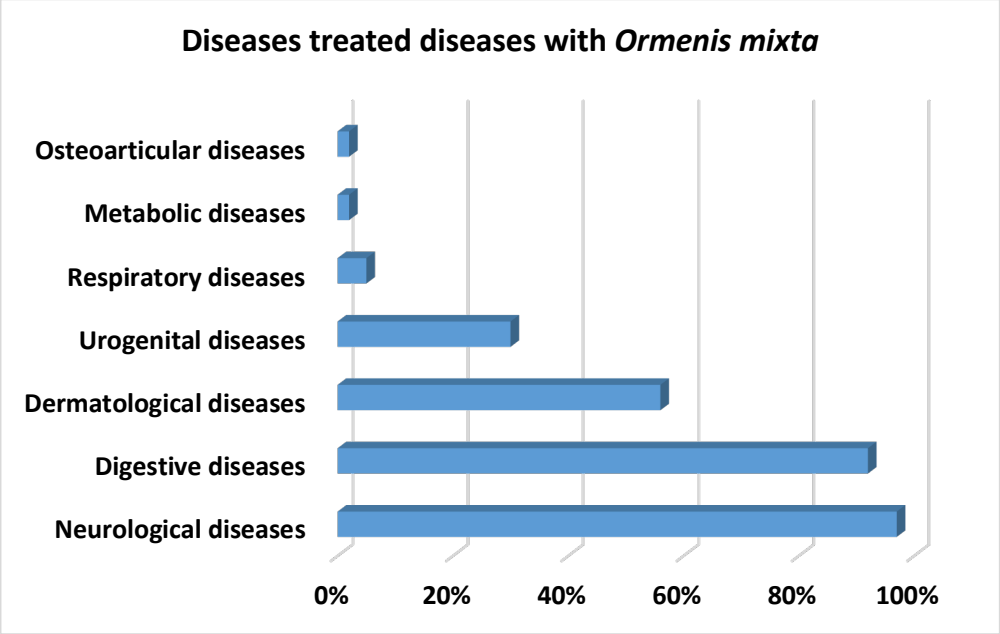

Figure 6. Percentage of the different diseases treated by *O. mixta*.

Literature review on bioactivities of *O. mixta*

A literature review was carried out to collect the recent information about the biological and pharmacological properties of *O. mixta*, which are presented in Table 3. Moreover, the main chemical compounds responsible for the pharmacological activities of *O. mixta* have been chemically structured in Figure 7. Indeed, *O. mixta* has been used as traditional therapy against many troubles such as the circulatory (low blood pressure, high blood pressure, and glycemia), the digestive tracts diseases (stomach pain, diarrheas, intestinal gases, and constipations), and the skin diseases (cook hair, facial skincare, eczema, burns, and wounds). It has also been recommended to rebalance the central nervous system, such as in the case of nervous breakdowns; and to short come liver and stomach light and colitis produced by *colibacillus* (Elouaddari *et al.* 2019).

Recently, many studies have focused on health benefits and biological activities of *O. mixta* extracts, including antibacterial, antifungal, anti-inflammatory, anti-nociceptive, and cytotoxic properties (Benteldjoune *et al.* 2019, Chraibi *et al.* 2021, Elouaddari *et al.* 2019, Ouedrhiri *et al.* 2018).

Several works have assessed the antibacterial activity of *O. mixta* against a number of reference bacterial strains (American type culture collection (ATCC)), using qualitative and quantitative approaches. Indeed, Ouedrhiri and his colleagues (2018) showed that *O. mixta* EO exhibits an interesting antibacterial effect against Gram-positive bacteria, *Staphylococcus aureus* ATCC 29213 (IZ= 9.33 ± 0.57 mm, MIC= 2 %), and *Bacillus subtilis* ATCC 3366 (IZ=11.33 ± 0.57 mm, MIC= 2 %), while no effect was noticed against Gram negative bacteria such as *P. aeruginosa* and *E. coli*. Moreover, a recent study carried out by Chraibi *et al.* (2021) reported the same results, where the Gram-negative bacteria (*E. coli* ((IZ=8.66 ± 0.57mm, MIC=0.25%, MBC=0.5%v/v)) are more resistant than the Gram-positive bacteria (*S. aureus* IZ=14 ± 1mm, MIC= 0.125%, MBC=0.5% v/v).

Furthermore, *O. mixta* EO has also been found to exert antifungal effects against *Candida tropicalis* with an IZ equal to 9 ± 0.84 mm (Chraibi *et al.* 2021). The results of the broth microdilution assays showed that *O. mixta* EO has an effective antimicrobial activity against the studied yeast with MIC= 0.25% and MBC= 0.5% (v/v) (Chraibi *et al.* 2021).

Generally, few studies have explored other biological activities of *O. mixta* EO comparing to antimicrobial investigations. Elouaddari *et al.* (2019) evaluated the antioxidant potential of *O. mixta* EO, using DPPH radical scavenging and 2,2′-azino-bis 3-ethylbenzothiazoline-6-sulphonic acid (ABTS) assays. Data showed that *O. mixta* EO exhibits an important reduction of the DPPH and ABTS radicals with an IC_{50} equal to 0.59 ± 0.11 mg/mL and 1.933 ± 0.048 mg/mL, respectively.

In addition, at different concentrations, the guaianolides derivatives isolated from *O. mixta* induced a significant reduction of nitric oxide release by macrophages as well as an inhibition of pro-inflammatory mediators' production such as cyclooxygenase (COX) (Benteldjoune *et al.* 2019).

Phytochemistry of *O. mixta*

According to the previous data, scientists were more interested in examining the phytochemistry of volatile oils from different biological parts of the *O. mixta* plant. Actually, the quantitative chemical composition of aqueous extract of *O. mixta* aerial part collected in Sidi Yahya, North-West Morocco, has been examined by Hajjaj and his collaborators using the following chemicals and reagents: Alkaloids with Mayer and Dragendoff's reagents, Saponins (frothing test) and tannins ($FeCl_3$), flavonoids (NaCl and HCl), terpenoids (Salkowski test), and anthraquinones (H_2SO_4). In short, the phytochemical screening showed that the aqueous extract obtained from *O. mixta* aerial parts are rich in Tannins, Saponins, Terpenoids, flavonoids and alkaloids and does not contain Anthraquinones (Hajjaj *et al.* 2017).

Regarding the chemical composition of the volatile oil of this plant, Zrira *et al.* (2007) examined the qualitative composition of *O. mixta* whole plant EO from two different Moroccan regions, Kénitra and Salé. The GC and GC-MS analysis showed that the main oil component of *O. mixta* from Kenitra was santolina alcohol which is associated with yomogi alcohol. While the major oil compounds of *O. mixta* from Salé were santolina alcohol, artemesia alcohol and yomogi alcohol. Moreover, the EOs contained sesquiterpenes mainly represented by germacrene D, *epi*-α-Muurolol and α-cadinol, with slight variation.

In addition, Chraibi *et al.* (2021) studied the EO obtained by hydrodistillation from *O. mixta* collected in Taounate region. The GC-MS and GC-FID analysis showed an important percentage of oxygenated monoterpenes and moderate quantity of sesquiterpene hydrocarbons and oxygenated sesquiterpenes. Santolina alcohol was the principal compound. Also, other components were detected at low amounts: farnesene, Epi-α-muurolol, α-pinene, Artemisia alcohol, and α-cadinol. Whereas, Ouedrhiri *et al.* (2018) revealed through the GC-MS analysis, D-germacrene, 1,8-cineole, and cis-methyl isoeugenol as main compounds of the EO from *O. mixta* Fresh leaves and stems, collected in Taounate region.

Furthermore, Elouaddari and his co-workers (2015) extracted the EO separately from the leaves and flowers of *O. mixta* via hydrodistillation and analyzed them by GC-MS. *O. mixta* plants were collected from five different regions of Morocco (Kenitra, Tamesna, Sidi allal lbahraoui, Settat, and Benguerir). Cluster analysis showed a significant variation in the chemical composition of *O. mixta* leaves and flowers. In fact, the major compounds of flowers were camphor, 2-tridecanone, and *trans*-β-farnesene. While the main compounds of leaves were *trans*-nerolidol, camphor, and β-myrcene.

Table 3. Synopsis about biological activities of *O. mixta*.

Activity	PU	Extract	Study type	Method	Key result	Chemical compound	References
Antibacterial	AP	EO	*In vitro*	DDM BDM against *Bacillus subtilis* ATCC 3366, *S. aureus* ATCC 29213, *P. aeruginosa*, *E. coli* ATCC 25922	IZ=(9.33 ± 0.57-11.33 ± 0.57) mm MIC=2% v/v	D-germacrene, 1,8-cineole and α-pinene	(Ouedrhiri *et al.* 2018)
Antioxidant	AP	EO ME AE	*In vitro*	DPPH ABTS	IC_{50} = 0.59 ± 0.11 - 1.933 ± 0.048 mg/mL IC_{50} = 2.030 ± 0.006 mg/mL	γ-terpinene, myrcene, borneol, terpinen-4-ol, and D-limonene	(Elouaddari *et al.* 2019, Ouedrhiri *et al.* 2018)
Antifungal	AP	EO	*In vitro*	Determination of MFC by BDM against *Candida tropicalis*	IZ= 9 ± 0.84 mm MFC= 0.25/0.5 % (v/v)	Santolina alcohol	(Chraibi *et al.* 2021)
Cytotoxic	AP	EO ME	*In vitro*	The colorimetric MTT assay using mouse *myeloma* cell line	IC_{50} = 85.27 - 125.5 µg/mL	borneol, camphor and caryophyllene	(Elouaddari *et al.* 2019)
Anti-corrosive	WP	extract solution	*In vitro*	EIS and potentiodynamic polarization techniques	An effective inhibition for the corrosion of steel in sulphuric acid media	Chamazulene, a-bisabolol, bisabololoxides A and B, polyacetylenes (*cis*- and *trans*-spiroethers), flavonoids (apigenin-7-glucoside and luteolin-7-glucoside)	(Abdel-Gaber *et al.* 2006)
Anti inflammatory	AP	Guaianolides	*In vitro*	NO release and COX-2 expression in macrophages treated with lipopolysaccharide (J774A)	1 - 3, and 7 were able to inhibit NO release, while all were able to inhibit COX-2 expression with different potencies.	1 - 3, and 7 guaianolides	(Benteldjoune *et al.* 2019)

GSH: glutathion; DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate; ABTS: 2,2 -azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; WP: whole plant; MFC: minimum fungicidal concentration; IC_{50}: median inhibitory concentration ; EIS: Electrochemical impedance spectroscopy.

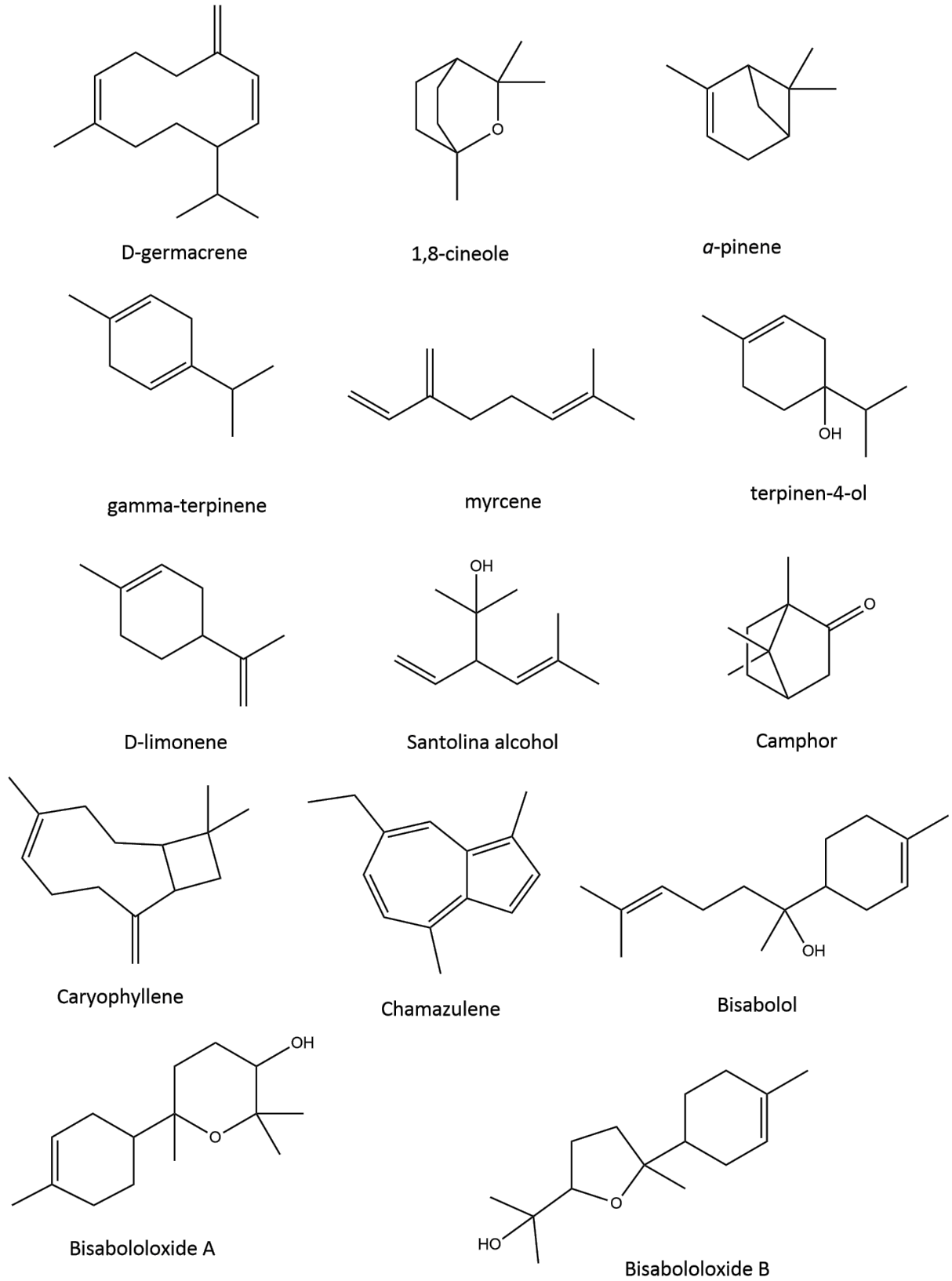

Figure 7. The main chemical compounds responsible for the biological activities of *O. mixta*.

Another study on the volatile oil from air-dried aerial parts of wild *Cladanthus mixtus* (Syn. of *O. mixta*) from two different regions of Morocco, Bouznika and Oujda, identified for the first time via GC and GC/MS analysis two compounds, namely 2-Methyl-2-trans-butenyl methacrylate which characterizes the chemotype of the plant collected from Bouznika, whereas trans-β-farnesene typifies the chemotype from Oujda (Elouaddari *et al*. 2014).

Interestingly, Benteldjoune *et al*. (2019) isolated five new guaianolides (1-5) and four (6-9) known sesquiterpenes from *O. mixta* aerial parts to assay their anti-inflammatory potential. The structural determination of these compounds was obtained by *nuclear magnetic resonance* (NMR) spectroscopic data and MS experiments.

Diagnosis, treatment results, and side effects of the two medicinal plants

Regarding the treatment results of *O. mixta*, 81% of respondents confirm that there is an improvement after being treated by the plant remedies, and 18% strongly believe in the healing power of this plant, while only 1% of the population declared that treatment with *O. mixta* was ineffective. In addition, no side effects have been reported following the therapeutic use of *O. mixta*.

As for *A. herba-alba*, 95% of the population reported improvement after using *A. herba-alba* remedies, while 3.5% reported recovery and 1.5% mentioned ineffective treatment. Moreover, 32% of respondents notified ulcers (32%), allergies (16%) or both (20%) as side effects of *A. herba-alba*, whereas 68% of the population indicated that there are no side effects due to *A. herba-alba* usage.

In the case of the two studied medicinal plants, the diagnosis is usually made by the population itself (93% of the population), while 17% resort to herbalists since they are well informed in herbal medicine and have inherited the profession of herbalism from their parents and elderly relatives. Hence, more precaution is needed for the consumption of these plants, especially in the case of *A. herba-alba* for which some adverse effects have been reported by the population of the study area.

Conclusion and perspectives

The present study aims to valorize two common plants widely used by the population of the Taounate region: *A. herba-alba* and *O. mixta*. Thus, this work made it possible to draw several conclusions about the ethnobotanical reality of the studied medicinal plants. Indeed, data revealed that married people are more interested in medicinal plants especially women, and the age group of (40-60) years habitually use herbal remedies. Also, the study showed that leaves, stems and flowers are the most used parts for the remedy preparation. These plants parts are mainly prepared as a decoction and principally administered via oral route. In addition, these medicinal plants are involved in the treatment of digestive, metabolic, neurological, respiratory, genitourinary, dermatological, and osteo-articular diseases. According to the population surveyed, no adverse effects associated with the use of *O. mixta* were reported, however *A. herba-alba* could cause ulcers or allergies when used at a high dose. Therefore, an in-depth phytochemical study of the different extracts of *A. herba-alba* and *O. mixta* are required to identify other secondary metabolites which could serve as active principles in the pharmaceutical industries. Further *in vivo* investigations are needed to validate the *in vitro* results of the biological activities studied so far. Besides, other pharmacological properties should become evident to confirm the therapeutic uses of these plants. Moreover, toxicological analysis is in demand to verify the posology of the plant extracts. Preclinical and clinical trials are equally needed to study the efficacy and safety of the plants.

Declarations

List of abbreviations: SPSS: System Package for Social Sciences, *Artemisia herba-alba* Asso: *A. herba-alba, Ormenis mixta* (L.) Dumort: (*O. mixta*), EO: essential oil, AP: aerial part, DDM: disc diffusion method, BDM: broth dilution method, IZ: inhibitory zone, MIC: minimal inhibitory concentration, MBC: minimal bactericidal concentration, LC_{50}: Lethal Concentration 50, IL-6: interleukine-6, TNF: tumor necrosis factor, PGE2: *Prostaglandin E2,* NO: Nitric Oxide, ED_{50}: Effective dose 50, L: leaves, ME: Methanolic extract, MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, NI: not-identified, F: flowers, AE: Aqueous extract, GSH: glutathion, DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate, ABTS: 2,2 -azino-bis(3-ethylbenzothiazoline-6-sulfonic acid, WP: whole plant, MFC: minimum fungicidal concentration, IC_{50}: median inhibitory concentration, EIS: Electrochemical impedance spectroscopy, COX-2: cyclooxygenase-2, ROS: reactive oxygen species, GR: Glutathione reductase, GPx: Glutathione peroxidase, GST: Glutathione S-transferase, DNA: deoxyribonucleic acid, tp53: tumor *protein* 53, K-RAS: Kirsten rat sarcoma virus, TPC: total phenolic compound, GC: gas chromatography, GC-MS: gas chromatography-mass spectrometry, TLC:

Thin-layer chromatography, GF-FID: Gas Chromatography-Flame Ionisation Detector, ATCC: American type culture collection, *NMR*: *Nuclear magnetic resonance.*

Ethics approval and consent to participate: The data were collected with respect to confidentiality, anonymity, and consent. All respondents 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, active participation to methodology structuring, First draft manuscript writing, data analysis and interpretation. Nisrine Ech-chibani: Ethnobotany surveys conduction, data analysis and interpretation. 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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