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Egyptian Coniferous Plants: *Pinus canariensis*, *Cupressus lusitanica*, and *Cupressus arizonica*: Phytochemical Review, Biological Potentials, and Future Prospects

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Abstract

For many decades, conifers have been used for their ornamental, economic and medicinal importance. *Pinus canariensis, Cupressus lusitanica, and Cupressus arizonica* are three conifers cultivated in Egypt. These plants have different traditional uses for a variety of diseases such as liver, spleen, kidney, bladder, bone, joint diseases, bronchitis, wounds, toothache, and hair loss. This review article aimed to provide detailed scientific data on the chemical composition and pharmacological activities of these plants. Data from the literature on three plants were obtained using electronic databases such as Google Scholar, PubMed, and Scopus. The reported data showed differences in their essential oil composition due to different factors such as geographical origin, seasonal variations, and the organ used. Additionally, the analyzed studies confirmed that extracts and oils of the three plants have different biological activities as anti-bacterial, anti-dermatophytes, antifungal, antioxidant, anti-diabetic, anti-Alzheimer, and anti-aging. However, there is scarce information concerning their mechanism of action and their clinical studies. Therefore, further research on these issues is necessary in the future to understand the full therapeutic effect and pharmacological mechanisms of this medicinal species.

Keywords: Conifers; *Cupressus; Pinus;* Egypt*;* Phytochemistry; Pharmacology

1. Introduction

Coniferous forests are a renewable source of essential oils (EOs), which are found in a variety of plant organs: roots, needles/leaves, cones/seeds, wood/stem/twigs, bark, and berries [1]. They are woody plants with needle-shaped leaves that produce unisexual cones with bract scales. Pinaceae, Araucariaceae, Cupressaceae, Podocarpaceae, Cephalotaxaceae, Taxaceae, Phyllocladaceae, and Sciadopityaceae are among the commonly known coniferous families. Conifers comprise about 70 genera as *Taxus*, *Cupressus*, *Picea*, *Pinus*, *Cedrus*, *Araucaria*, and more than 600 species [2].

Genus *Cupressus* is a member of the Cupressaceae family. Different organs have been reported to be useful in the treatment of different diseases. Hemorrhoids, bleeding, varicose veins, asthma cough, spasms, diarrhea, rheumatism, common colds, piles, urinary tract ailments, and vaginal discharge are some examples [3]. In traditional medicine leaves and cones of *C. lusitanica* were used for the treatment of bone, joint diseases, liver, spleen, kidney, and bladder in Kenya. While used in postpartum and against hair loss in Cameroon. In Ethiopia, the decoction of the leaves was used in the treatment of toothache [4].

Genus *Pinus* is a unique member of the Pinaceae family. Different organs such as leaf, cone, bark, and resin are also used to treat different ailments such as bronchitis, tuberculosis, cold-influenza, and cough, and act as a diaphoretic, rubefacient, and antiseptic, while the resin is used in wound healing and injury [5].

There are different constituents present in EOs of conifers as terpenes (monoterpenes, sesquiterpenes and diterpenes). However, EOs composition could be variable depending on different factors such as organs used, climatic, seasonal variations, and geographic location as well as the time and harvesting period [6]. Added to that, lignans, nitrogenous compounds as alkaloids, polyphenols: flavonoids, flavanonols, flavones, biflavones, flavonols and flavan-3-ols, phenolic acids: benzoic acids, hydroxycinnamic acids, and stilbenes are all found in coniferous plants [7].

There are several coniferous species cultivated in Egypt related to different genera such as *Juniperus*, *Taxodium*, *Araucaria*, *Pinus*, and *Cupressus* [8]. Several review articles on various conifer genera, some of which are cultivated in Egypt, have recently been published, but there is some information lacking about some *Pinus* and *Cupressus* species specifically, the effect of different factors such as the part used, climatic and seasonal variations, geographic location,

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harvesting time and season, on their EOs composition and biological activities. Therefore, the current review article is focusing, for the first time, on detailed scientific data on three coniferous plants cultivated in Egypt: *Pinus canariensis*, *Cupressus lusitanica*, and *Cupressus arizonica*. In terms of chemical composition, pharmacological activities, the effect of several factors on the composition of their EOs, and the impact of these differences on their biological activities. In this way, this could result in different future viewpoints on their potential therapeutic benefits.

2. Methodology

The data were collected from different bibliographic sources, i.e., Google Scholar, PubMed, and Scopus without time limitation using the following keywords alone or in combination: *Cupressus*, *Pinus*, essential oil, plant extract, isolated compounds, phytochemistry, *in-vivo*, *in-vitro*, biological activities and the names of species *Cupressus lusitanica*, *Cupressus arizoncica*, and *Pinus canariensis.* The structures of compounds were drawn using ChemDraw Professional 15.0 program.

3. Phytochemical Composition

Different chemical classes of compounds have been detected/isolated in/from extracts of three plants under study (Figure 1). They are classified into:

3.1. Polyphenolic compounds

Polyphenolics represent natural antioxidants as they inhibit lipid peroxidation, cancer development, and microbial growth [9]. There are different polyphenolic compounds isolated and/or identified in investigated plant extracts related to different classes such as phenolic acids, flavonoids, biflavonoids, and lignans. In particular, flavonoids, phenolic acids, tannins, and lignans are widely distributed in coniferous species [10].

3.1.1. Phenolic acids

Phenolic acids are classified into hydroxybenzoic acids (C6–C1 structure) and hydroxycinnamic acids derivatives (C6–C3 side chain) [11]. Recently, Saber *et al* [12] have reported the presence of quinic acid using HPLC-PDA/ESI-MS-MS in *P. canariensis* alcoholic extracts.

3.1.2. Flavonoids

Flavonoids are the most widespread polyphenolics in nature and are widely present in conifers [13]. Flavonoids consist of a three-ring central structure (A, B, and C rings), accordingly, they were classified into different chemical classes [14]. They may be found as aglycones or in glycosidic form. They possess different pharmacological properties as anti-oxidative, anti-inflammatory, and anti-carcinogenic [15]. Using modern HPLC techniques, some flavonoids have been identified such as quercetin glucoside in *C. lusitanica*, quercetin rhamnoside in *C. lusitanica*, and *C. arizonica*, kaempferol-3-*O*-rhamnoside as traces in *C. lusitanica.* [16]

Recently, Saber *et al* [12] have reported myricetin deoxyhexoside, syringetin hexoside, isorhamnetin-*O*-hexoside, apigenin hexoside, kaempferol coumaroyl hexoside, laricitrin rutinoside, and di-*O*-*p*-coumaroyltrifolin using HPLC-PDA/ESI-MS-MS in *P. canariensis* alcoholic extracts. The structures of the identified flavonoids present in the different organs of the three studied plants are illustrated in Figure 2.

3.1.3. Biflavonoids

Biflavonoid is a natural secondary metabolite that contains two sets of flavonoid dimers which are linked by either a C-C or a C-O linkage [17]. Each flavonoid is composed of a 15C skeleton which is divided into two aromatic rings (A and B) that are linked by a heterocyclic ring with an unsaturated carbonyl chain [18]. Biflavonoids are considered one of the main classes present in conifers especially the *Cupressus* genus [19]. Cupressuflavone is reported as a marker for the genus [20]. Recently, Romani *et al* [16] have identified By HPLC-DAD cupressuflavone, amentoflavone, and robustaflavone in both *C. lusitanica* and *C. arizonica*, hinokiflavone, and methylrobustaflavone in *C. arizonica* leaves, Methylamentoflavone in *C. lusitanica* leaves. The structures of the identified biflavonoids present in the different organs of the three studied plants are illustrated in Figure 2.

3.1.4. Lignans

Lignans contain several types of phenylpropanoid (propylbenzene) molecules which are dimers formed of two coniferyl or sinapyl alcohol units linked together at the tails [21]. Lignans and their glucoside derivatives have numerous bioactivities in plants and animals as they gained growing interest due to their wide chemotherapeutic potency [22]. Cowan *et al* [23] have reported that from the chloroform extract of stems of *C. lusitanica* two lignans were isolated and identified as arctigenin and matairesinol. Recently, Saber *et al* [12] have reported the presence of lariciresinol hexoside using HPLC-PDA/ESI-MS-MS in *P. canariensis* alcoholic extracts. The structures of the identified lignans present in different organs of the three studied plants are illustrated in Figure 2.

3.1.5. Terpenes

Terpenes are isoprenoids that appear as the most important and largest group of phytochemicals in conifers. They are classified based on C5 units into, hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterpenes (C25), triterpenes (C30), tetraterpenes (C40),

polyterpenes (> C40) [24]. Recently, Saber *et al* [12] reported two diterpene acids, hydroxy-abietatrienoic acid, and isopimaric acid, using HPLC-PDA/ESI-MS-MS in *P. canariensis* alcoholic extracts.

3.1.6. Fatty acids

Fatty acids are important bio compounds that participate in complex metabolic pathways and thus play important biological roles [25]. Recently, Saber *et al* [12] have detected arachidonic acid and hydroxypalmitic acid using HPLC-PDA/ESI-MS-MS in *P. canariensis* alcoholic extracts.

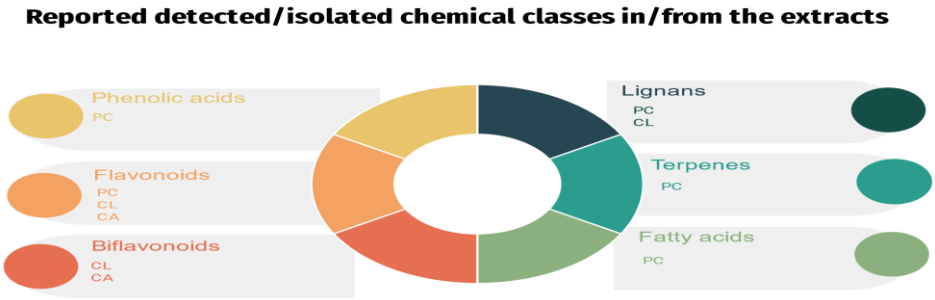


Fig. 1. Reported detected/isolated chemical classes in/from the extracts of the three studied plants .

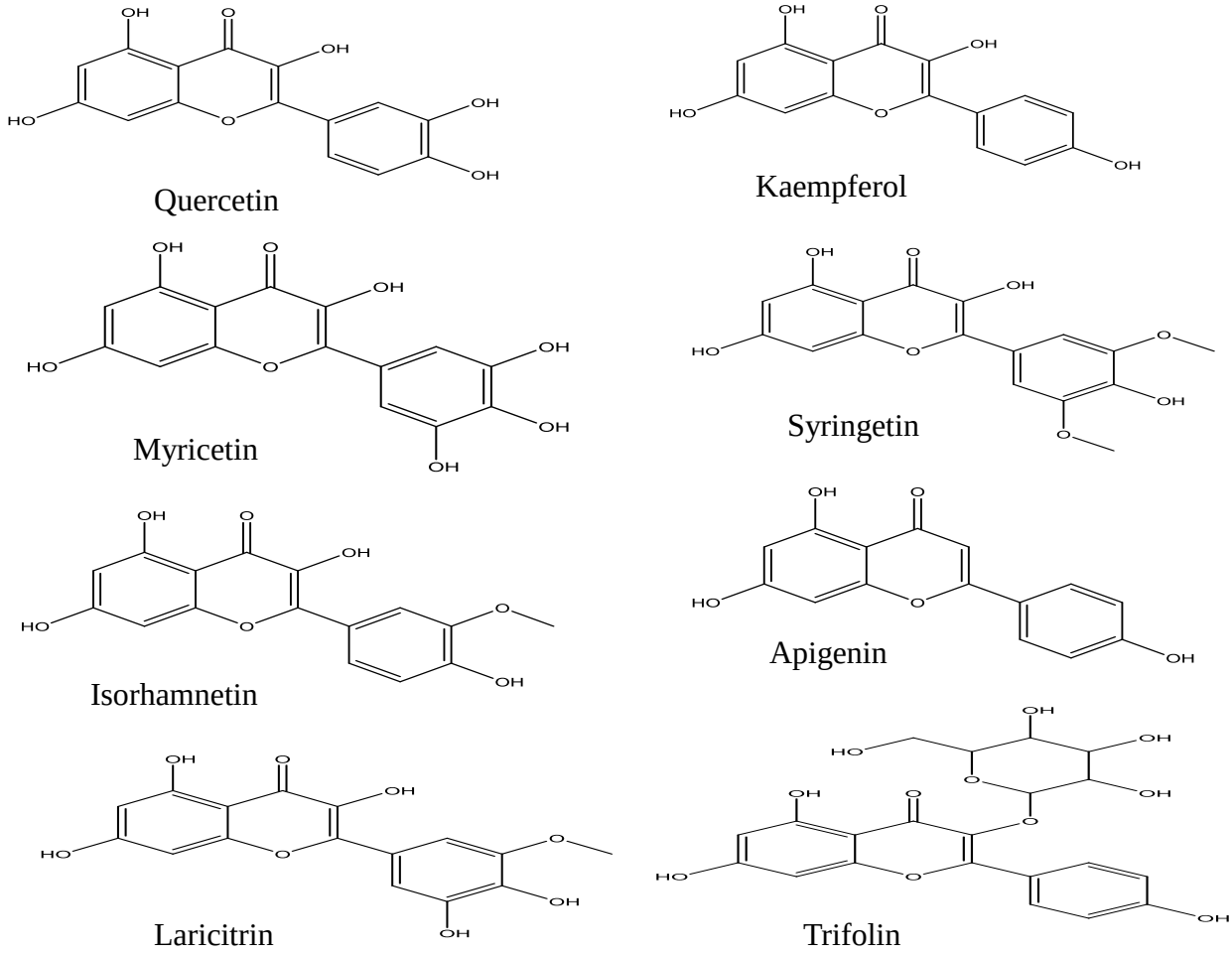
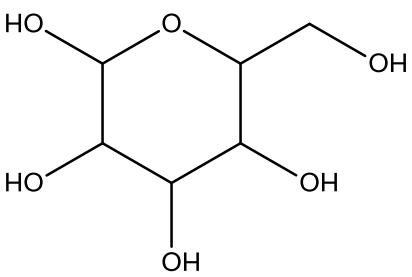
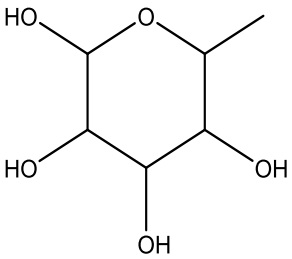


Fig. 2. Main compounds detected in the extracts of the three studied plants

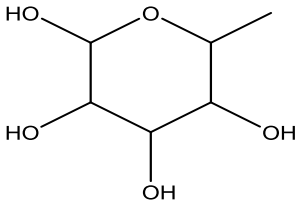
Flavonoids



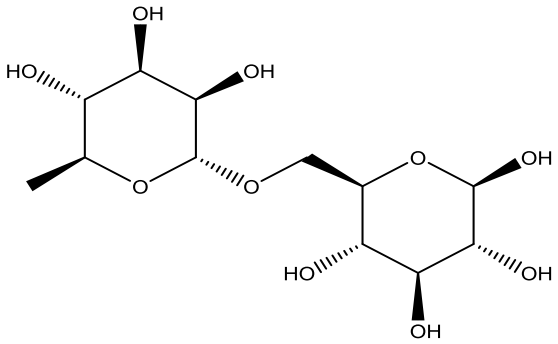
Glucose



Rhamnose



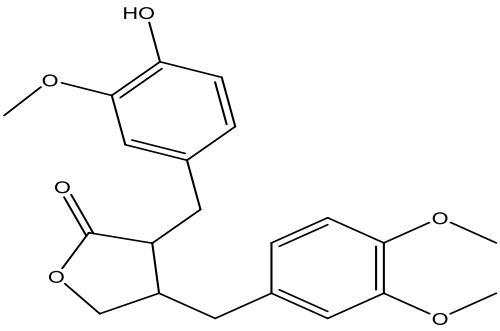
Deoxyhexose



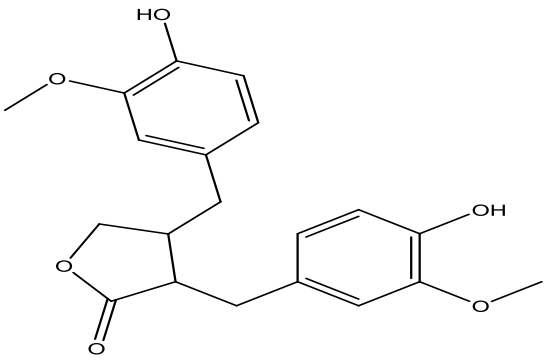
Rutinose

Main attached sugar units

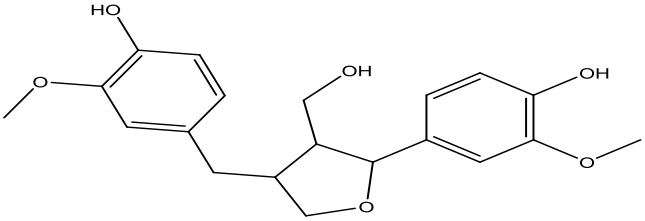
Fig. 2. Cont. Main compounds detected in the extracts of the three studied plants.



arctigenin



matairesinol



lariciresinol

Fig. 2. Cont. Main compounds detected in the extracts of the three studied plants.

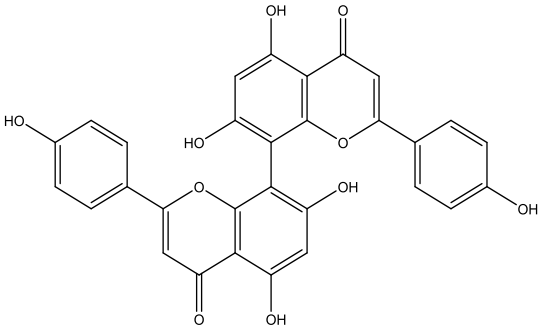
Lignans

3.2. Volatile Compounds

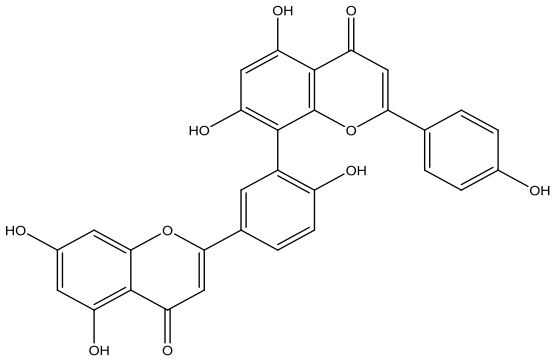
Essential oils (EOs) are multi-component natural systems comprised primarily of terpenes with certain non-terpene components. EOs and their components are widely used in human disease prevention and treatment [26]. Water or steam distillation, solvent extraction, expression under pressure, supercritical fluid, and subcritical water extractions are some of the techniques used to extract essential oils from various parts of the aromatic plant. Monoterpenes, one of the major classes present in volatile oils of coniferous plants are isoprenoids that consist of 10-carbon members and they are responsible for the odors of plants [27],[28]. They possess different uses in fragrances and pharmaceuticals [29]. Medicinally, they have anti-inflammatory, anti-nociceptive, anti-ischemic, immunomodulatory [30], anti-cancer and anti-microbial effects [31]. *α*-Pinene is a monoterpene widely distributed in higher plants such as conifers, Juniper species, and Cannabis species, It has an impact on a variety of biological processes as antibacterial, antifungal, anti-inflammatory, anti-oxidant, neuroprotective, anti-ulcerogenic and anti-tumor [32]. Volatile compounds identified in three plants under study are listed below in **Table 1**.

It summarizes the part used, type of extraction, analysis, date of collection, and essential oil % yield. Tables S1, 3, and 4 in supplementary material showed the major constituents present in each plant. The main detected volatile components are shown in Figure 3. Chemical classes of volatile compounds detected in the EOs of the three plants with their average % are shown in Figure 4.

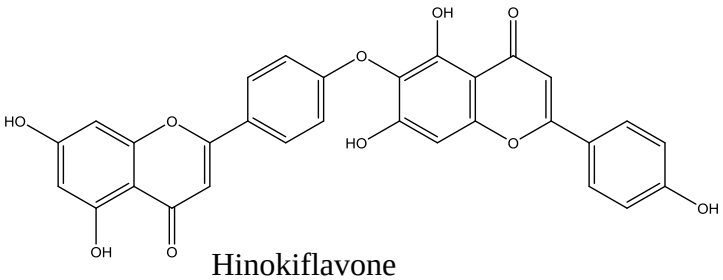
As illustrated in Figure 4 the chemical classes of volatile components in EOs of the three plants are monoterpene hydrocarbons with average percent (35-57%), then sesquiterpene hydrocarbons (13-50%), followed by oxygenated monoterpenes (1-23%) and the last three classes were oxygenated sesquiterpenes, diterpene hydrocarbons and oxygenated diterpenes (1-4, 0.2-1.8 and 0.3-0.5%, respectively). By comparing the composition and proportions of the compounds which constitute the studied essential oils (EOs), some significant variations were detected. These differences may be explained due to varied factors that have been reported to impact the composition of EOs extracted from plants. For example, The composition of EOs is affected by the organ used, climatic and seasonal variations, and geographic location beside the time and the season for harvesting [33].



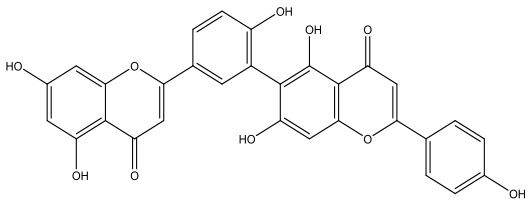
Cupressuflavone



Amentoflavone



Hinokiflavone



Robustaflavone

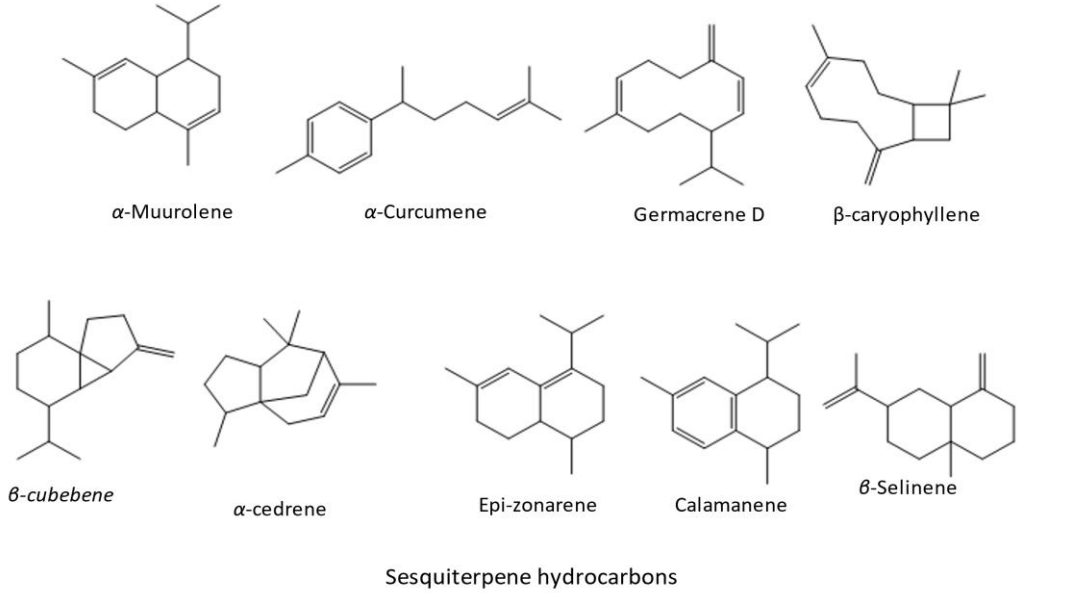


Fig. 3. Main detected volatile components of the three studied plants

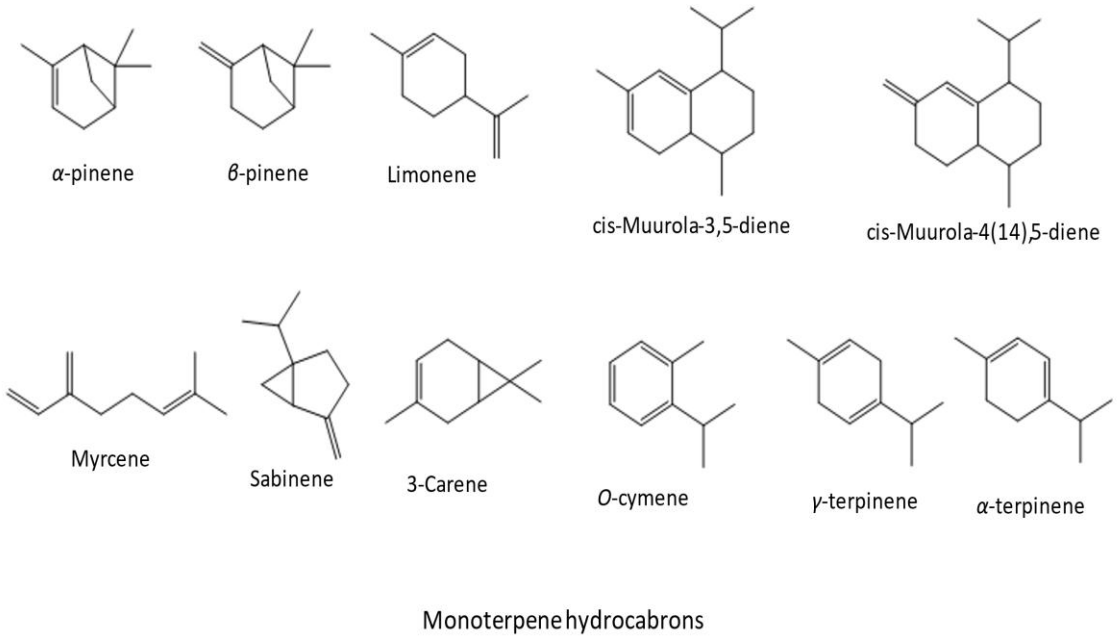


Fig. 3. Cont. Main detected volatile components of the three studied plants

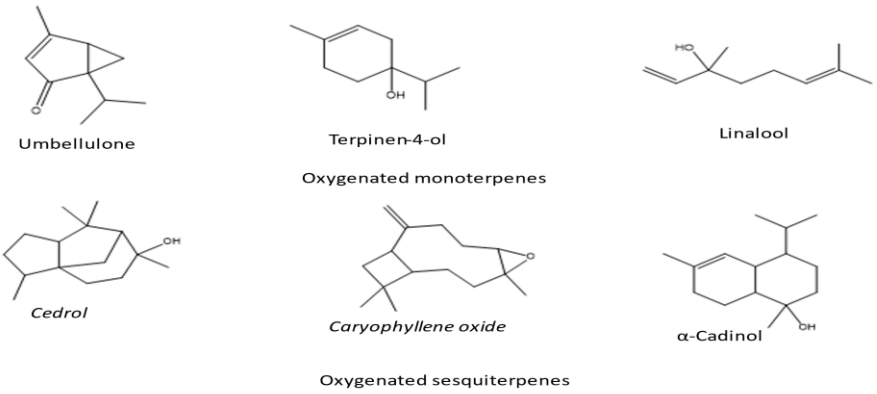


Fig. 3. Cont. Main detected volatile components of the three studied plants

Reported chemical classes of EOs components

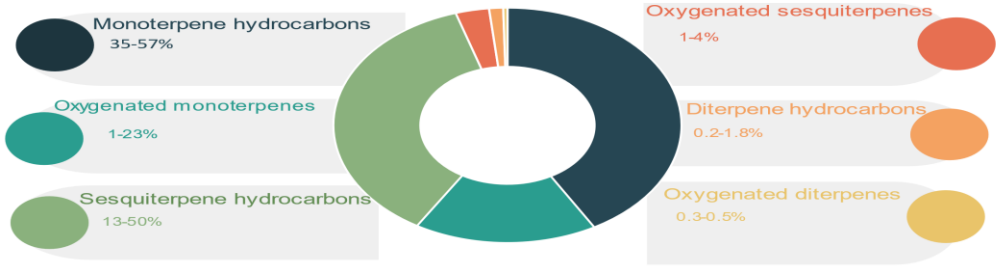


Fig. 4. Reported chemical classes of EOs components detected in the three plants with their average %.

Remarkably, the effect of geographical distribution was manifested in the case of *Cupressus arizonica* EOs. For instance, EOs extracted from female cone branchlets grown in the Himalayas and India (codes 20 and 21, supplementary material table S1) had nearly identical compositions [34]. The major constituents were umbellulone, limonene, and *α* -pinene (20.9-30.6, 8-12.9, and 7.1-8.1%, respectively). However, the percentage mentioned differs from the plant grown in South Carolina, Tunisia, and Italy (code 13,14,15, supplementary material table S1) in which the main constituent is *α*-pinene (68.5-79.7%) [35], [36], [37]. Likewise, despite using the same organ (leaves), some constituents were only detected in certain geographical places. In more detail, *β*-cubebene, was only detected in Tunisian leaves oil (code 6, supplementary material table S1) [36], whereas eicosane was only found in Iranian oil (code 4, supplementary material table S1) [38].

Similarly, in *P. canariensis* EOs we noticed differences in composition and quantity of oils from the same organ but different geographical origins. For example, *α*-Pinene and *β*-pinene were detected in oils from Algeria, Egypt, and Greece, respectively (code 33,40, and 38, supplementary material table S3), with some variation in composition. More specifically, *α*-pinene was represented (1, 72.3, and 14.6%, respectively) while *β*-pinene was represented (0.1, 15.7, and 3.2%, respectively). Aside from that, limonene, *β*-selinene, and cis-nerolidol were only found in Algerian oil, while *β*-caryophyllene was found in Algerian and Grecian oils but not in Egyptian oil [39], [40], [41].

Regarding the impact of using **different plant varieties**. (Code 1 and 2, supplementary material table

S1), are two different varieties of *C. arizonica*, grown in the same country (Tunisia). They had nearly identical compositions with minor differences in quantity, with *β*-cubebene, calmanene, and 14-norcadin-5-en-4-one representing (6.71, 4.5, and 2.78%, respectively) in var. arizonica and (0.32, 0.17, and 0.79%, respectively) in var. glabra [42].

Table 1: Part used, type of extraction, analysis, date of collection, Mass, place of collecting region, essential oil % yield present in each one.

Plant name	Code*	Part used, country	Type of extraction, analysis	Date of collecting	Essential oil % yield	Ref.
C. arizonica var. arizonica	1	Leaves, Tunisia	Hydrodistillation, GC-MS	-	-	[42]
C. arizonica var. glabra	2	Leaves, Tunisia	Hydrodistillation, GC-MS	-	-	[42]
C. arizonica	3	Leaves, Tunisia	Hydrodistillation, GC-MS	March. 2015	1.21% (v/w)	[45]
C. arizonica Greene	4	Leaves, Iran	Hydrodistillation, GC-MS	May- 2017	-	[38]
C. arizonica Greene	5	Leaves, Argentina	Hydrodistillation, GC-MS	Spring	0.78±0.03% (v/w)	[64]
C. arizonica Greene	6	Leaves, Tunisia	Hydrodistillation, GC-MS and GC-FID	Winter 2011	0.4%(v/w)	[36]
C. arizonica	7	Leaves, Italy	Hydrodistillation, GC-MS	November 1999	0.27%(w/w)	[37]
C. arizonica	8	Leaves, Greece	Hydrodistillation, GC-MS	June 2011	-	[65]
C. arizonica	9	Leaves, Morocco	Hydrodistillation, GC-MS	March 2017	0.85%(v/w)	[66]
C. arizonica Greene	10	Green twigs, Italy	Hydrodistillation, GC-MS	2016	0.6% (w/w)	[43]
C. arizonica var. glabra	11	Needle-twigs, USA	Hydrodistillation, GC-MS	September-October 2006.	-	[35]
C. arizonica	12	Female cones, Tunisia	Hydrodistillation, GC-MS	March. 2015	1.1% (v/w)	[45]
C. arizonica var. glabra	13	Female cones, USA	Hydrodistillation, GC-MS	September-October 2006.	-	[35]
C. arizonica Greene	14	Female cones, Tunisia	Hydrodistillation, GC-MS and GC-FID	Winter 2011	0.5%(v/w)	[36]
C. arizonica	15	Female cones, Italy	Hydrodistillation, GC-MS	November 1999	0.67%(w/w)	[37]
C. arizonica var. glabra	16	Male cones, USA	Hydrodistillation, GC-MS	September-October 2006.	-	[35]
C. arizonica	17	Cones, Morocco	Hydrodistillation, GC-MS	March 2017	1.29%(v/w)	[66]
C. arizonica	18	Branches, Tunisia	Hydrodistillation, GC-MS	March. 2015	0.85% (v/w)	[45]
C. arizonica	19	Branches, Italy	Hydrodistillation, GC-MS	November 1999	0.71%(w/w)	[37]
C. arizonica Greene	20	Branchlets with female cones, India	Hydrodistillation, GC-MS	September, 2011	1.0%(v/w)	[34]
C. arizonica Greene	21	Branchlets with female cones,	Hydrodistillation, GC-MS	September, 2011	1.7%(v/w)	[34]

		India				
C. arizonica var. glabra	22	Wood-bark, USA	Hydrodistillation, GC-MS	September-October 2006.	-	[35]
C. arizonica Greene	23	Stems, Tunisia	Hydrodistillation, GC-MS and GC-FID	Winter 2011	1.3% (v/w)	[36]
C. arizonica Greene	24	Fruits, Iran	Hydrodistillation, GC-MS	April to May 2020	-	[44]
C. arizonica	25	Aerial parts, Tehran	Hydrodistillation, GC-MS	-	1.30% (w/v)	[67]
C. lusitanica Mill.	26	Leaves, Cameroon	Hydrodistillation, GC-MS	August 2010	0.32%	[46]
C. lusitanica Mill.	27	Leaves before and at flowering stage, Cameroon	Hydrodistillation, GC-MS	June 2003	0.33%	[47]
C. lusitanica Mill.	28	Leaves, Kenya	Hydrodistillation, GC-MS	August, 2012	0.35%(v/w)	[48]
C. lusitanica Mill.	29	Leaves, Kenya	Hydrodistillation, GC-MS	December, 2019	-	[49]
C. lusitanica Mill.	30	Leaves, Cameroon	Hydrodistillation, GC-MS	October, 2018	0.676%	[50]
C. lusitanica Mill.	31	Fruits, Cameroon	Hydrodistillation, GC-MS	December 2003	0.50%	[47]
C. lusitanica Mill.	32	Flowers, Cameroon	Hydrodistillation, GC-MS	March 2004	0.10%	[47]
P. canariensis	33	Needles, Algeria	Hydrodistillation, GC-MS	May 2002	0.3%	[39]
P. canariensis Sweet ex Sprengel	34	Needles, Spain	Hydrodistillation, GC-MS	February 1999	0.3%	[68]
P. canariensis	35	Needles, Morocco	Hydrodistillation, GC-MS	July, 1995	0.16%	[69]
P. canariensis	36	Needles, Greece	Hydrodistillation, GC-MS	May, 2011	-	[70]
P. canariensis	37	Needles, Tunisia	Hydrodistillation, GC-MS	January 2017	0.5 ± 0.1 % (v/w)	[71]
P. canariensis	38	Needles, Greece	Hydrodistillation, GC-MS	October 2006	-	[41]
P. canariensis Sweet and Sprengel	39	Needles, Greece	Hydrodistillation, GC-MS	-	-	[72]
P. canariensis	40	Leaves, Egypt	Hydrodistillation, GC-MS	March, 2018	0.23% (w/w)	[40]
P. canariensis	41	Seeds, Algeria	Hydrodistillation, GC-MS	April, May and June 2010	0.28%	[51]

*Order of codes in each plant depends on the organ used, - = Not determined, *C. arizonica* = *Cupressus arizonica*, *C. lusitanica* = *Cupressus lusitanica*, *P. canariensis* = *P. canariensis*, Ref. =Reference

Moreover, different compositions in EOs due to differences in **organs used** can be noticed. In oils originating from *C. arizonica* from green twigs in Italy and fruits in Iran (code 10 and 24, supplementary material table S1), respectively, *α*-pinene was represented (41 and 17.1%, respectively). Additionally, trans-muurola-3,5-diene and calmanene were only found in fruits, while cis-cadina-1(6),4-diene was only found in green twigs [43], [44]. Similarly, oils extracted from green twigs in Italy and female cones in Tunisia (code 10 and 12,

supplementary material table S1) differed in the composition and percentage of *α*-pinene, *δ*-3-carene. They were found in concentrations of (41%, 0.9 and 60.5, and 15.3%, respectively). Furthermore, cis-cadina-1(6),4-diene was detected in green twigs only, while *α*-muurolene was detected in female cones only [43], [45]. Besides, oils of male cones, needle-twigs, wood-bark, and stems (code 16,11, 22, and 23, respectively, supplementary material table S1) showed a difference in *α*-pinene percentage (22.5, 20.7, 40.7 and 76.6%, respectively) [35], [35], [35], [36].

Likewise, the quantity of components in *C. lusitanica* EOs of different organs differed. Like that, oils derived from leaves and flowers (code 26 and 32, supplementary material table S2) contained *α*-pinene, myrcene, δ-3-carene, linalool, umbellulone, and terpinene-4-ol (0.6, 0.4, 0.5, 6, 6, 6.3% and 64.5, 6, 6.5, 0.3, 0.3, 1.9% in leaves and flowers, respectively). Moreover, some differences in composition were observed, such as germacrene D, epi-zonarene, cis-calamene, and di-epi-*α*-cedrene being detected only in leaves (18.5, 8.2, 8.2, and 4.9%, respectively) [46], [47].

Added to that, codes (28,29 and 30, supplementary material table S 2) are all oils originating from leaves, with code 30 coming from Cameroon and codes 28 and 29 coming from Kenya. Even that, we can notice a difference between them such as *α*-thujene, *β*-pinene, *α*-Terpinene, and umbellulone were detected only in Cameroonian oil whereas *α*-Terpinene, cis-Muurola-4(14),5-diene and amorpha-4,7(11)-diene were detected only in Kenyan oil. Linalool, Sabinene, γ-terpinene, and terpinene-4-ol, on the other hand, were detected in both with a slight difference in quantity as sabinene, γ-terpinene, and terpinene-4-ol were in concentrations (20.8, 7.5 and 16.8%, respectively) in Cameroon, and (3.4-8.1, 0.2-1.7 and 1.3-6.1%, respectively) in Kenya [48], [49], [50].

Similarly in *P. canariensis* EO obtained from Algerian **seeds** (code 41, supplementary material table S3), in which *α*-pinene was absent and Limonene was dominant with 10.8%. It is remarkably found that, there is a much difference between its composition and other **needles** oils [51].

Table 2: Antibacterial, Antifungal and larvicidal activities of the three oils.

Name	Activity	Part used	Source	Major constituents	Method, positive control	Microorganisms	Results	Ref.
Cupressus arizonica Greene	Antimicrobial	Leaves	Tunisia	*α*-Pinene, Umbellulone, cis-Muurola-4(14),5-diene, Limonene, cis-Muurola-3,5-diene	Agar disc diffusion, Levofloxacin (positive control)	Gram (+) bacteria: *Staphylococcus aureus* and *Enterococcus faecalis* Gram (-) bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* Clinical isolates: *Klebsiella pneumoniae* and *Streptococcus pneumoniae*	For EO: MIC: 0.38-23.6 µg/ml MBC: 0.38-23.6 µg/ml Disc diameter inhibition zone (DD): 10-27 mm For positive control: MIC: 0.30-4.88 µg/ml MBC: 0.30-19.53 µg/ml DD: 11-34 mm	[45]
C. arizonica Greene	Antimicrobial	Branches	Tunisia	*α*-Pinene, δ-3-Carene, Limonene, Myrcene	Agar disc diffusion, Levofloxacin (positive control)	Gram (+) bacteria: *S. aureus* and *E. faecalis* Gram (-) bacteria: *E. coli*, *P. aeruginosa*, *S.*	For EO: MIC: 0.76-11.8 µg/ml MBC: 0.8-23.6 µg/ml DD inhibition	[45]

						typhimurium Clinical isolates: *K. pneumoniae* and *S. pneumoniae*	zone: 9-28 mm For positive control: MIC: 0.30-4.88 µg/ml MBC: 0.30-19.53 µg/ml DD: 11-34 mm	
C. arizonica Greene	Antimicrobial	Cones	Tunisia	*α*-Pinene, *δ*-3-Carene, Terpinolene	Agar disc diffusion, Levofloxacin (positive control)	Gram (+) bacteria: *S. aureus*, *E. faecalis* Gram (-) bacteria: *E. coli*, *P. aeruginosa*, *S. typhimurium* Clinical isolates: *K. pneumoniae* and *S. pneumoniae*	For EO: MIC: 1.47-11.8 µg/ml MBC: 2.95-23.6 µg/ml DD inhibition zone: 8-19 mm For positive control: MIC: 0.30-4.88 µg/ml MBC: 0.30-19.53 µg/ml DD tested at a concentration of 20 ml/disc: 11-34 mm.	[45]
C. arizonica Greene	Antibacterial	Cones	South Lebanon	nd	Agar disc diffusion, Tetracycline (positive control)	*Staphylococcus epidermidis* and *E. coli*	DD inhibition zone (mm): For EO: 8 mm-10 mm For positive control: 18-22 mm MIC values For EO: 200 µg/ml for both strains	[73]
C. arizonica Greene	Antibacterial	Green twigs	Italy	nd	Agar well diffusion, Gentamicin,	*E. coli*, *Listeria monocytogenes*, *S. aureus*, *C. albicans*, P. *fluorescens*	DD inhibition zone (mm) (8 ± 0.1) to (10 ± 0.4)	[43]

					ciprofloxacin and fluconazole disks (positive control)			
C. arizonica var glabra	Larvicidal	leaves	Greece	*α*-Pinene, trans-Muurola-3,5-diene, Umbellulone	*In-vitro*	*Aedes albopictus*	$LC_{50:}$ 64.8 mg/L $LC_{90:}$ 78.2 mg/L	[65]
C. arizonica var. glabra	Antifungal	Leaves	Tunisia	*α*-Pinene, Umbellulone, β-Cubebene, Calmanene	*In-vitro*	*Saccharomyces cerevisiae* , *S. cerevisiae* rad4, *S. cerevisiae* yap1, *S.cerevisiae* apn1, *Candida albicans*, *C. glabrata* 8D, *C. dubliniensis* CIPO 82, *C. parapsilosis* 28 B, *C. tropicalis* IGC 3097 and *C. bracarensis* NCYC 3133	MIC (µl/ml): 1×10^{-3} to 5×10^{-2}	[42]
C. arizonica var. Arizonica	Antifungal	Leaves	Tunisia	*α*-Pinene, Umbellulone, Terpinen-4-ol, α-Cedrene	*In-vitro*	*Saccharomyces cerevisiae* , *S. cerevisiae* rad4, *S. cerevisiae* yap1, *S. cerevisiae* apn1, *Candida albicans*, *C. glabrata* 8D, *C. dubliniensis* CIPO 82, *C. parapsilosis* 28 B, *C. tropicalis* IGC 3097 and *C. bracarensis* NCYC 3133	MIC (µl/ml): 1×10^{-2} to 5×10^{-2}	[42]
C. arizonica	Insecticidal	Aerial parts	Tehran	*α*-Pinene, Limonene, Myrcene, Sabinene, Umbellulone and epi-Bicyclosesquiphellandrene	*In-vitro*	Adult rice weevil (*Sitophilus oryzae* L.)	Medium lethal concentration (LC_{50}): 172.30 µl/L air	[67]
Cupressus lusitanica Mill	Antimicrobial	Leaves	Costa Rica	*α*-pinene, limonene, isobornyl acetate and cis-muurola-4(14),5-diene	Microbroth dilution, Geneticin and Amphotericin B (positive control)	*Bacillus cereus*, *Aspergillus niger*	MIC: 78-1250 µg/ml	[74]

C. lusitanica Mill	Antimicrobial	Leaves	Cameroon	Germacrene D, terpinen-4-ol, umbellulone, linalool	Agar disc diffusion, Gentamicin and nystatin (positive control)	Gram (+) bacteria: *E. faecalis* and *S. aureus* Gram (−) bacteria: *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa*, *S. typhi* and *Shigella flexneri* Fungi: *C. albicans*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, *C. parapsilosis* and *C. tropicalis*	DD inhibition zone (mm): For crude oil: Bacterial strain: 11–18 Fungal strain: 7–14 Fractions: Bacterial strain: 7-10 Fungal strain: 6-14 MIC (% v/v): For crude oil: Bacterial strain 1.25-10% Fungal strain: 0.16-1.25%	[46]
C. lusitanica Mill	Insecticidal	leaves	Cameroon	Umbellulone and *α*-pinene	Instant contact toxicity bioassay, Space fumigation bioassay and Instant repellence bioassay	*Tribolium castaneum*, *Acanthoscelides obtectus*, *Sitotroga cerealella* and *Sitophilus. zeamais*	LC_{50} values (% v/w) of EOs after 24–168 h: 0.02-1.21 LC_{50} values (µl/L air) of EOs 24 h post-fumigation: 3.17-29.11	[48]
C. lusitanica Mill	Insecticidal and anti-plasmodium	Leaves	Cameroon	Sabinene, terpinen-4-ol and *α*-pinene	*In-vitro* radioisotopic method	Adult female *Anopheles gambiae s.l.*, *Plasmodium falciparum*	Lethal concentration 95 (LC_{95}) and mortality (%) of *Anopheles gambiae s.l.* larvae: 90.52 and 76-91.6 respectively IC_{50} (ppm) on *P. falciparum:* 44.86	[50]
C. lusitanica Mill	Antidermatophytic	Leaves	Cameroon	Umbellulone, Germacrene D, *α*- pinene	Agar dilution, Griseofulvin and amphotericine B	*Tricophyton mentagrophytes*, *T. rubrum*, *Microsporum audouinii* and *M. langeronii*	% inhibition of EO: Leaves 31.16-100% Fruits 5.61-70.19%	[47]

					(positive control)			
Pinus canariensis	Antibacterial and antifungal	Needles	Tunisia	*δ*-cadinene, amorphene	Agar well diffusion for antimicrobial, micro-dilution broth for MIC	Gram (+) bacteria: *S. aureus* and *E. faecalis* Gram (-) bacteria: *E. coli* and *E. cloacae* Yeast strains: *C. albicans*, *C. parapsilosis* and *C. sake* Mould strains: *Penicillium* spp., *A.* niger and *Alternaria* spp.	MIC (µg/mL) 0.0024-0.024 and MBC (µg/mL) 0.0024	[53]
P. canariensis	Antibacterial	Needles	Tunisia	Germacrene-D, Limonene, *α*-Pinene	Paper-disc agar diffusion, Gentamicin discs (Positive control) For MIC Micro-well dilution, Gentamicine (Positive control)	Gram (+) bacteria: *S. aureus* Gram (-) bacteria: *P. aeruginosa,* and *E. coli* Clinical isolates: Haemophilus *influenzae*, *H. parainfluenzae* and *K. pneumonia*	DD inhibition zone (mm): EO: 6-8 Gentamicine: 22.4-35.6 MIC µg/mL: EO: 264 Gentamicine: 0.6-6 MBC µg/mL: EO: 528 Gentamicine: 2.5-24	[71]
P. canariensis	larvicidal activity and repellency	Needles	Greece	*α*-pinene, Germacrene D	Larval susceptibility test	*A. albopictus*	LC_{50} (mg/L): >200	[70]

Additionally**, Seasonal variations** have a significant impact on the composition of *C. lusitanica* oils. More specifically, three oils were collected from leaves in Cameroon during August, July, and June (Code 26,27[c] and 27[d], supplementary material table S2). They showed different compositions and quantities between them. More deeply, *α*-pinene was (5.3-7.4%) in June and (0.6%) in August, sabinene was (1-4.9%) in June and (0.3%) in August, linalool was (1.3-2%) in June and (6%) in August. Along with, umbellulone concentration showed significant seasonal variation as it represented (17.3-18.3%) in June and (6%) in August, terpinene-4-ol was (2-2.6%) in June and (6.3%) in August. Besides that, Germacrene D was (18.5%) in August and (2.5-8.5%) in June, epi-zonarene was (8.2%) in August and (0.7-5%) in June. Additionally, some components were detected in only one season such as cis-Muurola-3,5-diene, which was absent in August but present in June (0.4-4.2%), γ-Curcumene, which was absent in August but present in June (1.5-3%), and cis-Calamenene and di-epi-*α*-cedrene, which were present in August (8.2, 4.9%, respectively) but absent in June [46], [47].

4. Biological activities

4.1. Biological activities of extracts

Different biological activities have been reported for extracts of the three plants under study (Figure 5). They are classified into:

A) Antibacterial, anti-dermatophytes, and antifungal

Different coniferous plants have been reported to exert antimicrobial activity against different bacterial strains [28]. Recently, Ndossi and Chacha [52] have studied *in-vitro* antibacterial and antifungal activity by microdilution method. Minimum inhibitory concentration (MIC) of *C. lusitanica* extract of different organs (leaves, seed cover, and seeds) using *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *K. oxytoca*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *S. kisarawe* and two strains of fungi *Cryptococcus neoformans* and *Candida albicans* were calculated. For MIC in mg/mL, the chloroform extract of leaves ranged between 6.25-12.5, the ethyl acetate extract of leaves ranged between 1.56-12.5, while the methanolic extract of leaves ranged between 1.56-25. The seed cover chloroform extract was 6.25-25, while its ethyl acetate extract was 6.25-12.5 and its methanolic extract ranged between 3.12-25. Different extracts of seeds showed MIC ranging between 3.12-more than 25. On the other hand, positive controls such as gentamicin and fluconazole gave MIC (0.19-3.15 and 6.25, respectively).

Moreover, Kuiate *et al* [47] have studied the antidermatophytic activity using the agar dilution method against *Microsporum audouinii*, *M. Langeronii*, *M. canis*, *Trichophyton rubrum*, and *T. tonsurans* of five fractions of hexane leaf extract of *C. lusitanica* by flash-chromatography. GC/MS analysis showed *α*-pinene as a major component in fraction one while in fractions two and three epi-bicyclosesquiphellandrene was the major one. While the other fractions showed eicos ane, tricosane, and heptacosane.

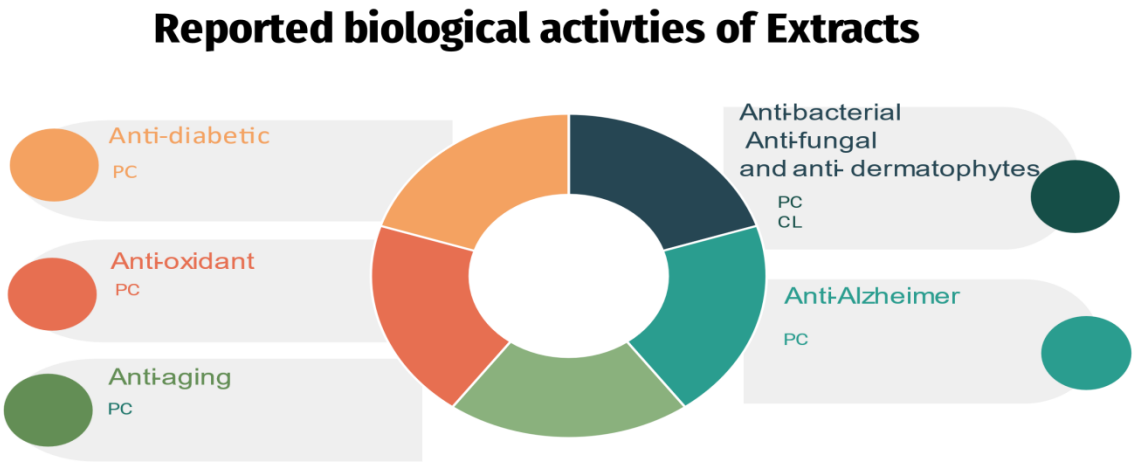


Fig. 5. Reported biological activities of extracts of the three plants.

Additionally, Ghazghazi *et al* [53] have studied the antimicrobial activity, by using the agar diffusion method, of *P. canariensis* needles which were obtained from Tunisia on two gram-negative bacteria (*E. coli* and *Enterobacter cloacae*), two gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*), three yeast strains (*Candida albicans*, *C. parapsilosis*, and *C. sake*) and three mould strains (*Penicillium* spp., *Aspergillus niger*, and *Alternaria* spp.). MIC and Minimum Bactericidal Concentration (MBC) were calculated in µg/mL and ranged between 0.001-10000 and 0.001-1000 µg/mL, respectively.

B) Antioxidant

Oxidative stress is defined as an imbalance between the production of reactive oxygen species, known as free radicals, and antioxidant defense [54]. Antioxidants reduce oxidative stress in cells, therefore they are used in the treatment of many human diseases such as cardiovascular disease, inflammatory diseases, rheumatoid arthritis [55], and cancer [56]. Extracts of

various plant organs and their constituents have been studied as a natural source of antioxidants. This includes seeds, fruits, leaves, and other plant organs [57]. Koutsaviti *et al* [58] have studied the antioxidant activity of both the organic and hydroethanolic needles' extracts of *P. canariensis* using the luminol chemiluminescence (LCL) assay and IC_{50} in (µg/mL) was calculated which was 0.29 ± 0.05 and 0.20 ± 0.01, respectively.

C) Anti-diabetic

Diabetes mellitus is characterized by high plasma glucose levels caused by insufficient insulin or insulin resistance, or both, resulting in metabolic changes in carbohydrates, lipids, and proteins [59]. El-Manawaty and Gohar [60] have studied the antidiabetic effect by the *in-vitro* α-glucosidase inhibitory activity of 95% methanolic extract of fruits and leaves of *P. canariensis* cultivated in Egypt and they gave 99 and 91 % activity on enzyme at 25 ppm, respectively and by calculation of $IC_{50,}$ it was 4.37±0.7 and 11.27±1.9, respectively.

D) Anti-Alzheimer

Alzheimer's disease (AD) is a neurodegenerative disorder that causes mental decline and cognitive impairment in elderly people. Naturally occurring compounds found in various parts of plants and/or marine sources, such as flavonoids, polyphenols, alkaloids, and glycosides, may potentially protect against neurodegeneration and improve memory and cognitive function [61]. Recently, a potential anticholinesterase activity of Egyptian *P. canariensis* needles' 70% ethanolic extract showed IC_{50} around 60 µg/ml against Donepezil which was around 40 µg/ml [12].

D) Anti-aging

Skin aging is a multisystem degenerative process influenced by different endogenous and exogenous factors such as genetics, hormone and metabolic processes, chronic light exposure, pollution, chemicals, and toxins [62]. Saber *et al* [12] have studied the *in-vitro* telomerase activity of Egyptian *P. canariensis* needles with 70% ethanolic extract which caused an increase in telomerase activity and telomerase reverse transcriptase (TERT) level in normal human melanocytes cells compared to the negative control.

4.2. Biological activities of oils:

Different biological activities have been reported for EOs of the three plants under study (Figure 6). They are classified into:

A) Antibacterial, Antifungal, and larvicidal activities

Naturally, essential oils play a vital role in attracting insects to promote pollen and seed spread or repelling others. Furthermore, essential oils may act as antibacterial, antivirals, antifungals, insecticides, and herbicides [63]. Three oils have been reported to possess antibacterial, antifungal, and larvicidal activities against different strains which were summarized in Table 5. From the summarized data, we can notice that Tunisian *C. arizonica* EOs exhibited almost the same antibacterial activity with comparable MIC values despite using different organs (leaves, branches, and cones). On the other hand, EO extracted from Tunisian cones is much different in MIC value than South Lebanon cones despite using the same antibacterial method, agar disc diffusion, and same bacterial strains and that may be due to geographical variations.

More intriguingly, despite using the same bacterial strains and the same organ (needles) from the same country (Tunisia), *P. canariensis* EOs showed a noticeable difference in MIC values 0.0024-0.024 to 528 µg/ml and that may be due to differing in EOs components and/or the difference in the antibacterial methods used.

B) Anti-nociceptive and anti-inflammatory

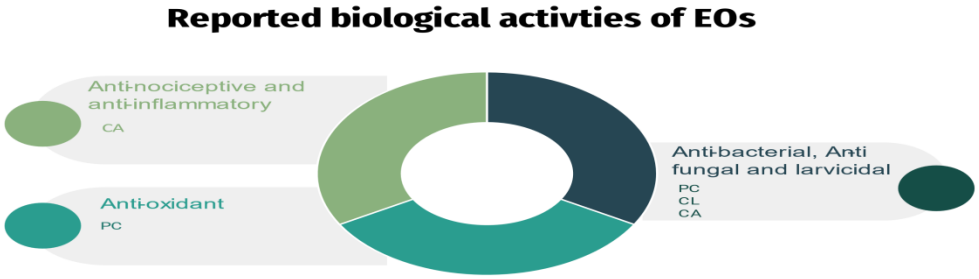
Inflammation is a multi-dimensional immunovascular response to different triggers such as pathogens, irritants, injury, and infections. When an inflammatory agent is present, cell membranes activate phospholipase A2, resulting in the release of arachidonic acid which led to the release of inflammatory mediators such as cytokines, serotonin, histamine, prostaglandins, and leukotrienes. Followed by, an increase in vascular permeability and allowing leukocytes to migrate to the site of inflammation [30]. Recently, Fakhri *et al* [44] have studied the *in-vivo* anti-nociceptive and anti-inflammatory effects of EO of Iranian *C. arizonica* Greene fruits, in which *α*-pinene, myrcene, *δ*-3-carene, *β*-pinene, and limonene were the major ones using *in-vivo* model by formalin test and carrageenan-induced inflammation model. The results showed that the anti-nociceptive effects of EO possess a dose-dependent pattern and exhibited a time-dependent anti-inflammatory activity.

C) Antioxidant

Essential oils can scavenge free radicals so they may be useful in the prevention of diseases such as brain dysfunction, cancer, heart disease, and immune system declining states [63]. Koutsaviti *et al* [58] have studied the antioxidant effect of EO isolated from

needles of *Pinus canariensis* isolated by hydro-distillation from the National Garden of Athens, in October 2006 using Peroxy-Oxalate Chemiluminescence Assay and showed a significant effect with IC_{50} 1.00 ± 0.08 µg/mL

Fig. 6. Reported biological activities of EOs of the three plants



5. Conclusion and Future Trends:

In this review article, the phytochemical analysis and pharmacological activities relative to extracts and oils of three coniferous plants cultivated in Egypt, *Pinus canariensis*, *Cupressus lusitanica*, and *Cupressus arizonica*, were studied. Different volatile chemical classes have been detected in their EOs, monoterpene hydrocarbons with average percent (35-57%), then sesquiterpene hydrocarbons (13-50%), followed by oxygenated monoterpenes (1-23%), and the last three classes were oxygenated sesquiterpenes, diterpene hydrocarbons and oxygenated diterpenes (1-4, 0.2-1.8 and 0.3-0.5%, respectively). Variations in their essential oil composition due to varied factors such as geographical origin, seasonal variations, organs, and seasons were observed. Additionally, different classes of phytochemical compounds have been detected/isolated in/from their extracts such as phenolic acids, flavonoids, bioflavonoids lignans, terpenes, and fatty acids. Concerning their pharmacological activities their oils and extracts exhibited several activities as anti-bacterial, anti-dermatophytes, antifungal, antioxidant, anti-diabetic, anti-Alzheimer, and anti-aging. Interestingly, despite using the same species and organ from the same country, some biological activities produced different results, which could be attributed to differences in EOs components. However, data are scarce regarding these species in many fields, and it can be noticed that not all the reported biological uses are supported by an in-depth phytochemical analysis that can explain them. So, in this sense, many studies into phytochemicals are still required especially for their extracts of different organs, and more efforts are needed to confirm their traditional uses and evaluate the clinical potential of medicinal compounds. Additionally, studies on their oils' yields, compositions, and percentages are needed using more advanced techniques rather than hydrodistillation methods and the effect of these techniques on their biological activities. Finally, we hope that this review article may help and provide a further reason to study the three species in more detail.

Conflict of interest:

The authors have no conflicts of interest to declare.

List of abbreviations

AD, Alzheimer's disease; DD, Disc diameter inhibition zone; EOs, Essential oils; GC-MS, Gas Chromatography-Mass Spectrometry; HPLC-PDA/ESI-MS-MS, High-Performance Liquid Chromatography-Diode Array Detection-Electrospray Ionization Tandem Mass Spectrometry; IC50, Half maximal inhibitory concentration; LC50, Medium lethal concentration; LC95, Lethal concentration 95; LCL, luminol chemiluminescence, MBC, Minimum bactericidal concentration; MIC, Minimum inhibitory concentration.

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