Review

Pistacia lentiscus: from phytopharmacology to scientific explanations on its anti-inflammatory and antimicrobial capacity

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Abstract: There is an increasing interest in revisiting plants for drug discovery proving scientifically their role as remedies. Pistacia lentiscus (PL) is a wild-growing shrub rich in terpenoids, which are pharmacological appealing. The more recurrent components in the oil are represented by α-pinene, terpinene, caryophyllene, limonene, and myrcene. High concentration of polyphenols enriches the extracts. PL-extracts showed in vitro and in animal model strong anti-inflammatory and anti-oxidative activities. The anti-inflammatory activity mainly occurs due to inhibition of NF-kB pathway or directly toward the proinflammatory cytokines, or arachidonic acid cascade against COX-2 and LOX. The antimicrobial activity of PL essential oil and extracts includes among others Staphylococcus aureus, Escherichia coli, periodontal bacteria and Candida sp.. In conclusion, the biological properties, and particularly the anti-inflammatory and anti-microbial capacity, propose PL as a new safe pharmaceutical agent.

Keywords: essential oils, water extracts; ethanol extracts; periodontal bacteria, Candida, natural antimicrobials; natural anti-inflammatory; Sardinian plants, pharmaceutical plants.
1. Introduction

The undesirable side effects of antibiotics in addition to increasing microbial resistance have created a demand for new alternative molecules [1]. Also, non-steroidal anti-inflammatory drugs (NSAIDs) or even steroids, often inducing toxic side-effects [2-3] have gained further interest in safe molecules presenting anti-inflammatory character [4].

On these bases, there is an increasing attention in revisiting plants for drug discovery proving scientifically their role as popular remedy to diseases.

The capacity of essential oils (EO) from plants is related to the presence of different chemical classes among which terpenoids, also called terpen or terpenes, are promising agents in prevention and treatments of diseases [5]. Terpenoids are pharmacologically versatile: they are lipophilic, interact with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled receptors, second messenger systems and enzymes [6]. Terpenoid values, eventually potentiated by using nanotechnology [7-8], are attracting researchers to further explore them with the intent to improve human health.

In this contest, *Pistacia lentiscus* (PL) is a wild-growing shrub rich in terpenoids [9]. PL includes numerous wild and cultivated species, distributed in the Mediterranean and Middle Eastern areas. PL has been utilized for centuries by communities for social, culinary, and ritual purposes as well as for medicinal intent.

Despite the fact that many researches deeply documented the pharmaceutical properties of the resin (better known as mastic or mastix) derived from PL var. chia Desf. [10-11], scientific data regarding PL oil or extracts of leaves, fruits, and woods have been not summarized yet. Today, the scientific interest in these compounds is widespread as some studies underlined the potential benefit in inflammation, infections, and human health in general [12-15].

Given the above considerations, the purpose of this review was to screen the biological properties of PL EO and extracts of leaves, fruits, and woods, which are widely applied in the Mediterranean ethnopharmacology. Further, we revised the chemistry of PL growing in the different geographical areas and the scientific discovering, emphasizing the anti-inflammatory and antimicrobial abilities.

2. Botany and taxonomy

PL belongs to the genus Pistacia and the Anacardiaceae family, order Sapindales. Different classifications have been proposed regarding *Pistacia* genus. One of the most known is that of Zohary [16], who classified such genus into four main groups according to the characteristics of the leaf and nut morphology (Table 1).

Table 1 Taxonomy description of *Pistacia* genus (Zohary 1952)
In the Mediterranean area (Middle East and Europe), the three most represented species are the following:

1. *Pistacia vera*, which is characteristic of the temperate areas of Asia Minor, and grown abundant in Greece, Aegean Islands, and in Sicily (Italy). This species has been known since ancient times as attested in reports of the Old Testament. Also, there are notices of *Pistacia vera* by Persians and Greeks populations since the 6th and the 3th century B.C., respectively.

2. *Pistacia terebinthus*, originating from the island of Chios, has spread to all the Mediterranean coasts in the centuries. Today, it is mostly present in Portugal, Palestine and North Africa, in the Middle East of Asia till the western borders of India. In Italy, it is mainly found in the southern part of the peninsula and in Sardinia and Sicily.

3. *Pistacia lentiscus*, also known as mastic tree or lentisk (Fig 1).

**PL** represents one of the most typical shrubs in the Mediterranean maquis (shrubland) of Europe, Morocco, Turkey, Iraq, Iran [17]. In Italy, it is characteristic of sensitive ecosystem, like that of Sardinia [18], where it grows along the coast up to 700 meters above sea level. PL is an evergreen environmentally sustainable shrub. It is well adapted to harsh growing conditions, dryness and a warm environment, which all exercise an influence on the genotype and richness of secondary metabolites [9]. The plant is dioecious, where male and female flowers are on independent trees. The leaves are leathery, bright green and alternate. They are arranged in compound, pinnate whorls. The unisexual flowers are grouped in clusters. The globular fruit is a fleshy drupe, which ripe in fruits in August and ranges in colour from red to brown in view of the different degree of maturity [17]. PL can develop leaf galls due to insect attack, particularly aphid attacks [19]. Common aphid species, such as *Slavum wertheimae* and *Baizongia pistaciae L.*, manipulate the leaves to form tumorous galls to the safety and nutriment of their larvae [20]. The galls are rich in volatiles-like terpenes with abundance of monoterpenes, α -pinene and limonene [21]. Their chemical composition differs from that of the healthy leaves, which have in general higher content of sesquiterpenes [21].

### 3. Historical and cultural use

**PL** had a wide range of applications in the centuries. One of the oldest dates back to the Nuragic civilization (1800 to 238 BCE) [22] and was ascribed to Sardinian population: the oil obtained by cold-pressing the berries was widely used for social purposes *i.e.* home or votive lighting lamps, cooking, as well as a popular remedy (Camarda personal communication). This habit is attested by the presence of residues of "olium lentiscinum" often found during archeological excavations in "torcularia" (ancient oil mills) [23].

Today, **PL** is considered as an environment phytostabilizer due to the ability to detoxify the soil from harmful pollutants and heavy metals [24]. Furthermore, the plant represents
an important source to increase milk quality and dairy products from ruminants browsing Mediterranean maquis. [25].

4. Ethno-pharmacology

The ethnopharmacological survey on the medicinal use of PL is reported in Table 2.

Table 2. Ethnopharmacological uses of *Pistacia lentiscus*

| Ailment/uses                                                                 | Geographical area                      | References                                                                 |
|------------------------------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------|
| Oral cavity inflammation and infection, tooth ache, osteoarthritis, bronchitis, cough sedative, antipyretic, allergies, asthma, ulcerations, gastrointestinal disorders, wound healing, haemostatic | Sardinia, Italy                        | Camarda 1990, Ballero et al 2001, Sanna et al 2006, Palmese et al 2005, Barra 2007, Leporatti and Imperi 2007, Maxia et al 2008, Leonti et al 2009, Leonti et al 2015, Bullitta et al 2018, Di Rosa 2018 |
| Inflammation of the mouth, tooth ache, mycosis, herpes, refreshing feet       | Southern Regions of Italy (Calabria and Campania) | Scherrer et al 2005, Leporatti and Imperi 2007 |
| Hypertension and cardiac diseases                                             | Central regions of Italy (Abruzzi, Marche and Tuscany), Spain | Leporatti and Ghedira 2009, Villar et al 2008 |
| Analgesic, teeth strengthening, hypertension and cardiac diseases             | Spain                                   | Gras et al 2019, Villar et al 2008 |
| Antipyretic, astringent, eczema, paralysis, antimicrobial, throat infections, asthma, hypertension, cardiac diseases, paralysis, diuretic properties, renal stones, jaundice, antiatherogenic effect, antihepatotoxic, gastrointestinal diseases | Tunisia                                | Ben Douissa et al 2004, Leporatti and Ghedira 2009, Trabelsi et al 2012 |
| Stomach ache, dyspepsia, peptic ulcer, diarrhoea, rheumatism                  | Algeria                                 | Dellai et al 2013 |
| Hypertension, cardiac diseases and diabetes                                   | Morocco and North Africa                | El-Hilaly et al 2003, Aouinti et al 2012, Fakkich and Elachouri 2014 |
| Immuno-stimulant, antimicrobial                                               | Libya                                   | Elgubbi et al 2017 |
| Heartburn, soothes stomach, jaundice, wine preservative                      | Jordan                                  | Janakat et al 2002, Lev and Amar 2002 |
**Gum tissue strengthened, breath deodorizer, brain and liver tonic, gastrointestinal ailments**

Iran

Rahimi et al 2009, Farzaei et al 2013

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**Throat infections, asthma, eczema, stomach ache, renal stones, paralysis, diarrhoea, jaundice, anti-inflammatory, antimicrobial, antipyretic, stimulant, astringent**

Turkey

Duru et al 2003, Giner-Larza et al 2001

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As previously referred, there are few written indications on the medicinal use of the oil as crude compound, or of the extracts as well. Drinking water extracts and topical application of the extracts or even whole parts of the plant (woods or leaves) have been the most common means in antagonizing gastrointestinal, hepatic, urinary, pulmonary and neurological diseases. In fact, the medicinal value of PL in popular medicine covers a wide range of diseases mainly including inflammatory processes, and infections.

PL has been one of most used plants in Israeli and neighbouring countries traditional pharmacology [26]. In Jordan, it was commonly used to antagonize jaundice [27,28]. In Algeria, it is known as antimicrobial, antioxidant, hypotensive and hypoglycaemic agent [29,30]. In Morocco and Tunisia [31,32], PL has been largely used as a remedy against gastrointestinal, kidney and hepatic disorders, in addition to treat hypertension, diabetes, cardiac diseases, coughs, sore throats, and eczema. Similar applications are reported in Turkey [33] and in Iran [34, 35]. While, in Tunisia, Spain, and in the centre of Italy, it has emerged as an agent against hypertension and heart diseases [31-36].

Sardinian population has always found the medicinal properties of PL really appealing. A large number of publications report PL oil and water extracts as useful means against a wide variety of inflammatory diseases, infections, allergies [9, 22, 37- 40], ulcerations [41], gastrointestinal disorders [42], and as wound healing [38,43,44]. It is further interesting to note that Sardinian population administrated PL as a smoke obtained by burning or boiling the soft wood and leaves, particularly in the cases of osteoarthritis, bronchitis and allergies [22].

In addition, PL is still used as a remedy toward toothache and gingival inflammation by administering extracts from the leaves as oral mouthwash, beverages or by directly chewing the soft stems and leaves [22]. Similar beneficial effects have been reported by using the plants growing in the Southern (Campania) [23] and in the centre of Italy (Abruzzo, Marche and Toscana), in Tunisia [45] and in Spain [46].

The reports suggest PL molecules spread the anti-inflammatory and then, the regenerative properties, via epidermis or mucosal epithelium by rapid metabolism and redistribution. These properties have been attributed to the high account of monoterpenoids [47-51]. In this contest, the lipophilicity and lower molecular weight of these molecules [52], are important parameters to make them effective also at the Central Nervous System (CNS). Lipophilicity, molecular size, and protein complex formation make terpenoids capable to the passage to the CNS, where they were not only able to antagonize the inflammatory process [13,53,54] but also demonstrated relevant anticancer properties in neuroblastoma cell lines [14,55].

Regarding the veterinary use, in Sardinia, domestic animals are still treated by PL wood to combat gastrointestinal disorders, and by swab bark in wound healing procedures and skin diseases [56]. While, in Spain, the leaves are mentioned to treat specifically canine distemper [57].

All these reports highlight the important biological activities of the terpens fingerprint of PL [58]. However, variability in the concentration of monoterpenes, possible related to the
growing area of the plant, might explain the better ability of some chemical profile of PL oil or extracts in treating a disorder in comparison to another.

5. Phytochemical constituents

PL is constituted by a mixture of terpenoids, mainly monoterpenes and sesquiterpenes, which are also responsible for the characteristic smelling and flavouring of the plant. Terpenes family, also known as terpenoids or isoprenoids, comprises the most chemically and structurally heterogenous family of natural products, including more than 80,000 members among which steroids and carotenoids [59].

It has been reported that terpenes in PL are more genetically than environmentally related [60]. Nevertheless, environment of growing, seasonability of harvesting and kind of material (edible or not edible parts of the plant) have to be considered when explaining differences in chemistry of the oils and extracts [9] (Table 3).

| Main components of essential oils or plant extracts | Plant material | Test Assays | Origin | Authors |
|----------------------------------------------------|----------------|-------------|--------|---------|
| Essential oil                                      |                |             |        |         |
| α-pinene (16.89%), terpinen-4-ol (16.49%), sabiline (7.73%), α-phellandrene (7.39%), γ-terpinene (6.30%), β-pinene (4.30%) | leaves essential oil | GC-MS | Sardinia (Italy) | Milia et al. (2020) |
| myrcene (33.46%), α-pinene (19.20 %), limonene (6.58%), α-phellandrene (4.56%), γ-terpineol (3.73%), α-terpineol (3.58%) | leaves essential oil | GC-MS | Morocco | Bouyahya et al. (2019) |
| β-caryophyllene (12.8%), germacrene-D (9.6%), elemol (8.9%), α-terpineol (7.8%), γ-cadinene (7.1%), bornyl acetate (6.2%) | male flowers essential oil | GC-MS | Tunisia | Yosr et al. (2018) |
| α-limonene (28.7%), germacrene-D (23.7%), elemol (6.7%), β-caryophyllene (6.6%), α-pinene (6.0%), bornyl acetate (3.7%) | female flowers essential oil | GC-MS |        |         |
| α-limonene (18.8%), germacrene-D (13.1%), β-caryophyllene (8.8%), δ-cadinene (8.7%), γ-cadinene (6.2%), α-terpine (4.8%) | leaves of male plants at flowering essential oil | GC-MS |        |         |
| germacrene-D (20.7 %), δ-cadinene (15.6%), β-caryophyllene (12.1 %), γ-cadinene (6.6%), δ-cadinol (6.1 %), α-limonene (5%) | leaves of female plants at flowering essential oil | GC-MS |        |         |
| β-myrcene (75.6%), α-pinene (12.6%), α-limonene (3.2%), α-terpineol (1.4%), camphene (0.8%) | ripe fruits essential oil | GC-MS |        |         |
| terpinen-4-ol (25.2%), α-phellandrene (11.9%), β-phellandrene (10.2%), γ-terpinene (10.1%), α-pinene (7.6%) | leaves and twigs essential oil | GC-FID, GC-MS | Sardinia (Italy) | Marengo et al. (2017) |
| α-pinene (24.68-9.17%), 1-4 terpineol (14.89-7.12%), β-phellandrene (11.35-4.73%), β-pinene (8.64-1.15%), β-mircene (9.23-0.67%), α-terpineol (8.41-4.92%) | leaves essential oil | GC-MS | Tuscany (Italy) | Buriani et al. (2017) |
| Constituents                             | Sample Type        | GC-MS Parameters          | Location            | Authors                        |
|-----------------------------------------|--------------------|---------------------------|---------------------|-------------------------------|
| α-pinene (9.9%), limonene (8.5%), terpinen-4-ol (5.1%), β-caryophyllene (8.2%), germacrene D (11.9%), δ-cadinene (8.5%) | leaves essential oil | GC-FID, GC-MS          | Tunisia Aissi et al. 2016     |
| α-pinene (13.35%), α-phellandrene (10.12%), β-phellandrene (10.45%), sabinene (7.01%), germacrene-D (6.86%), β-caryophyllene (4.58%) | fruits essential oil | GC-MS                        | Tunisia Ben Khedir et al. 2016 |
| δ-germacrene (24.78%), myrcene (19.5%), α-cadinol (9.53%), γ-cadinene (5.59%), trans-caryophyllene (5.03%), limonene (4.84%) | fresh leaves essential oil | GC-MS                        | Greece Bampouli et al. (2014) |
| δ-cadinene (17.04%), α-amorphene (10.32%), δ-germacrene (9.01%), trans-caryophyllene (6.32%), α-cubebene (5.55%), naphthalene (4.13%) | dried leaves essential oil | GC-MS                        | Eastern Morocco Aouinti et al. 2013 |
| Germacrene D (19.9%), beta-caryophyllene (6.6%), alpha-pinene (6.3%), myrcene (3.9%), beta-phellandrene (3.7%) and alpha-humulene (2.4%). | leaves essential oil | GC-MS                        | Sardinia (Italy) Quartu et al. (2012) |
| Limonene (25.5–43.8%), myrcene (23.0–33.1%), α-pinene (20.0–34.2%) ranges shown by 17 natural populations | leaves essential oil | GC-FID, GC-MS, C-NMR         | Algeria Mecherara-Idjeri et al. (2011) |
| α-pinene (1.9-105 μg g⁻¹ dw), β-caryophyllene (54-198 μg g⁻¹ dw), δ-cadinene (15-186 μg g⁻¹ dw), cubebol (15-117 μg g⁻¹ dw), β-bisabolene (22.1-105 μg g⁻¹ dw), γ-muurolene (29.7-67.3 μg g⁻¹ dw) | leaves essential oil | GC-MS                        | Algeria Ait Saidi et al. (2011) |
| α-pinene (9.4-24.9%), terpinen-4-ol (6.8-10.6%), p-cymene (0.5-7.5%), limonene (9.0-17.8%), γ-terpinene (3.1-3.6%) | leaves essential oil | GC-MS                        | Sardinia (Italy) Maxia et al. (2011) |
| Myrcene (39.2%), limonene (10.3%), β-gurjunene (7.8), germacrene (4.3%), α-pinene (2.9%), muurolene (2.9%) | leaves essential oil | GC-FID; GC-MS                | Morocco Amhamdi et al. (2009) |
| α-pinene (14.81-22.59%), terpinen-4-ol (14.17-28.29%), β-myrcene (0.99-18.29%), p-cymene (14.79-16.22%), sabinene (2.51-8.13%), limonene (0.93-3.76%) | leaves essential oil | GC-MS                        | Sardinia (Italy) Barra et al. (2007) |
| Longifolene (12.8%), γ-cadinene (6.2%), trans-β-terpineol (5%), α-acorneol (4.6%), γ-muurolene (4.2%), β-pinene (3.7%) | aerial parts essential oil | GC, GC-MS                   | Algeria (Algiers) Dob et al. (2006) |
| Longifolene (16.4%), trans-β-terpineol (15.6%), terpinen-4-ol (7%), γ-muurolene (5.7%), β-pinene (3.3%), α-pinene (2.8%) | GC, GC-MS                | Algeria (Tizi-Ouzou)         |
| Compound          | GC/MS Analysis | Location     | Reference               |
|-------------------|----------------|--------------|-------------------------|
| α-pinene (19%), trans-β-terpineol (13.1%), sabinene (12.6%), β-pinene, (6.5%), (E)-β-ocimene (5.5%), longifolene (5.2%) | GC, GC-MS | Algeria (Oran) |                  |
| α-pinene (63%), β-mircene (25%), β-pinene (3.3%), limonene (1.5%), β-caryophyllene (0.9%), linalool (0.5%) perillene (0.5%) | mastic oil GC-MS | Greece Koutsoudaki et al. (2005) |                  |
| α-pinene (40%), β-mircene (9%), β-caryophyllene (5%), β-pinene (1.5%), limonene (1%) | mastic gum GC-MS | |                  |
| α-pinene (16.8%), 4-terpinenol (11.9%), β-phellandrene (8.9%), sabinene (5.7%), γ-terpinene (5.5%) and β-pinen (4.3%) | leaves essential oil GC-MS | Tunisia Ben Douissa et al. (2005) |                  |
| terpinen-4-ol (29.9%), α-terpineol, (11.6%), limonene (10.6%), (Z)-3-Hex-1-enyl benzoate (6.7%), α-pinene (4.2%), β-caryophyllene (3.2%) | leaves essential oil GC-MS | Turkey Duru et al. (2002) |                  |
| myrcene (20.58%), germacrene D (13.30%), E-caryophyllene (8.33%), α-cadinol (7.33%), t5-cadinene (7.00%) | leaves essential oil GC-MS | Greece Magiatis et al. (1999) |                  |
| myrcene (47.92%), germacrene D (15.46%), E-caryophyllene (4.75%) | twigs essential oil GC-MS | |                  |
| α-pinene (66.48%) | mastic gum GC-MS | |                  |
| α-pinene (79%), β-myrcene (3%) | gum essential oil GC-MS | Spain Boelens and Jimenez (1991) |                  |
| α-pinene (11%), β-myrcene (19%), α-terpineol + terpinen-4-ol (15%) | leaves essential oil GC-MS | |                  |
| α-pinene (22%), β-myrcene (54%) | unripe fruit essential oil GC-MS | |                  |
| α-pinene (11%), β-myrcene (19%) | ripe fruit essential oil GC-MS | |                  |

**Plant extracts**

| Compound                                                                 | GC/MS Analysis   | Location     | Reference               |
|--------------------------------------------------------------------------|------------------|--------------|-------------------------|
| 3,5-O-digalloyl quinic acid (13.48%), 3,4,5-O-trigalloyl quinic acid (6.05%), luteolin-3-O-rutinoside (7.84%), quercetin 3-O-di-hexose O-pentose (7.57%), quercetin 3-O-glucuronide (4.57%), epicatechin 3-gallate (4.5%), α-pinene (38.14%), β-pinene (9.53%), α-phellandrene (10.05%), D-limonene (11.91%), γ muurolene (7.95%), camphene (3.75%) | leaves extracts UHPLC-ESI-MS, GC-MS | Egypt El Bisbisyh et al. (2020) |                  |
| tannin derivatives (70.5%), myricetin derivatives (22%), quercetin derivatives (7.2%) | leaves ethanolic extract HPLC-DAD | Italy Gori et al. (2020) |                  |
| total phenolics (125.8 mg GAE/g DW), flavonoids (28.2 mg RE/g DW), condensed tannins (57.3 mg CE/g DW) | leaves extract at flowering stage GC-MS | Tunisia Yosr et al. (2018) |                  |
| 4-[3-[[2-hydroxybenzoyl] amino] anilino]-4-oxobut-2-enoic acid (28.96%), β-myrcene (11.47%), 3- | fruit oil extract GC–MS | Tunisia Ammari et al 2018 |                  |
In Table 3, it is reported that hydro-distillation using Clevenger-type devices, and ethanol extraction have been the more common methods to obtain the oil from the leaves, fruits and from the exudate of the trunk (mastic). However, the oil obtained by hydro-distillation and the extracts by solvents can have different organoleptic profiles and chemical compositions. These differences in turn will affect some properties, among which the antimicrobial capacity that is reported higher in a material solvent extracted in comparison to the hydro-distilled [61]. Additionally, the gas chromatography-mass spectroscopy (GC/MS) and the high-performance liquid chromatography (HPLC) have been the most useful means to quantify phytochemically the oils and extracts respectively [62]. Up to 64 chemical constituents have been reported in PL EO fingerprint, in addition to other fractions that cannot be quantified by the assays [15]. Interestingly, some of these terpenoids are constituent fractions of Cannabis sativa [51], and called “non-cannabinoid terpenoids”. In PL oil, non-cannabinoid terpenoids are more likely represented by α-pinene, myrcene, limonene, (E)-β-caryophyllene and γ-terpinene (Table 3). They are also included in the list of “terpene super classes” [51]. Furthermore, it is appealing to report that when non-cannabinoid terpenoids reach a concentration equal or higher 0.05% in an oil, they can confer pharmacological properties to such an oil, which can be classified as pharmaceutical active [6].

In view of the prevalent fractions of monoterpenes and oxygenated sesquiterpenes, the EO can be grouped in different chemotypes [17]. In this regard, the recurrent higher amount of α-pinene (16.89-19.5%) and terpinen-4-ol (7.7-16.49%) in comparison to the other compounds, allowed to classify the oil from the leaves of PL growing in Sardinia as α-pinene/terpinen-4-ol chemotype [9, 15]. Similarly, the Greek oil from PL leaves is α-pinene/terpinen-4-ol chemotype [63]. Nevertheless, the simultaneous existence of different chemotypes in a place can be justified by dissimilar geographical sites of harvesting in that country. An example is represented by the Corsican chemotype, which is expressed by three main phenotypes: the first is α-pinene/terpinen-4-ol; the second is terpinen-4-ol/limonene; and the third is myrcene-rich (88%) [9]. Very characteristic is the

| Phenolic composition of seed oil (concentrations not showed) | HPLC-DAD/MSD | Tunisia | Mezni et al. 2018 |
| oleic acid (53.3%), palmitic acid (28.6%), linoleic acid (13.7%), stearic acid (1.39%), palmitoleic acid (1.3%) | GC-MS | Tunisia | Mezni et al. 2014 |
| 46 secondary metabolites, qualitative phenolics composition | LC-ESI-MS/MS | Italy | Pacifico et al. 2014 |
| 46 compounds (most abundant flavonoids, phenolic acids and their derivatives) | HPLC-ESI-QTOF | Algeria | Rodriguez-Perez et al. 2013 |
| oils, fatty acids and sterols | GC-MS | Tunisia | Trabelsi et al. 2012 |

| Cyanidin 3-O-glucoside (71%), delphinidin 3-O-glucoside and cyanidin 3-O-arabinoside (28-31%) | HPLC-DAD-MS | Apulia (Italy) | Longo et al. 2007 |
| 3,5-O-digalloyl quinic acid (26.8 mg/g DW), 3,4,5-O-trigalloyl quinic acid (10.3 mg/g DW), 5-O-galloyl quinic acid (9.6 mg/g DW), myricetin 3-O-rhamnoside (6.8 mg/g DW), myricetin 3-O-rutinoside (4.5 mg/g DW), myricetin glucuronide (3.9 mg/g DW) | HPLC-DAD, HPLC-MS, NMR | Italy | Romani et al. 2002 |

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high content of δ-3-carene (65%) in the Egyptian oil [64], while the monoterpen terpinen-4-ol, together with α-pinene and the sesquiterpene myrcene are among the higher represented fractions in the chemistry of PL EO from Spain, Morocco and Turkey [65-67]. Conversely, α-pinene (65 - 86%) and β-myrcene (3%) are the major fractions to characterize the oils of mastic from plants growing in Spain [65]. And, the bioactive triterpenes are the most important compounds in such a resin with high role against the oxidative stress [68].

Regarding the sesquiterpenes, limonene, α- and β-caryophyllene, D-germacrene, δ-cadinene and α-cadinol, β-bisabolene, β-bourbonene and Caryophyllene oxide, they have shown extremely variable concentrations in PL EO [9, 15, 64, 65].

Further comprehensive studies have been conducted analysing methanol and alcohol extracts of PL leaves, at the same time investigating on the chemical profile and efficacy of the polyphenol content. In this regard, an interesting analysis was recently carried out by Romani and co-workers [69]. Using ethyl acetate and methanol fractions of PL leaves and semi-preparative HPLC, HPLC-photodiode array detection and HPLC-MS analysis, together with NMR analysis, the authors identified high polyphenol content in the extracts, which represented 7.5% of the leaf dry-weight. Further, three major classes of secondary metabolites were identified (i) gallic acid and galloyl derivatives of both glucose and quinic acid; (ii) flavonol glycosides, i.e. myricetin and quercetin glycosides; and (iii) anthocyanins, namely delphinidin 3-O-glucoside and cyanidin 3-O-glucoside. These findings suggest PL extracts as an important source of bio-molecules of relevant biological properties. Particularly, the high content of galloyl derivates, equal to 5.3% of the leaf dry-weight, was indicated for the high activity of PL to inhibit the HIV-1 lifecycle by targeting key HIV enzymes [70, 71] and in cancer therapy [72]. Myricetin derivatives, which in the extracts were 1.5% on a dry weight basis, exhibited relevant pharmacological activities in regard to the generation of apoptosis in cancer cells [73, 74]. Additionally, the HPLC with diode array coupled to an electrospray ionization mass spectrometry and the use of a negative ionization mode, recognized 46 different compounds in the methanol extracts of PL leaves from plants growing in Algeria [75]. Among the new 20 compounds characterized for the first time, there have been included important antioxidant agents in preventing diabetic complications, managing intestinal inflammatory response, cholesterol absorption and lipid metabolism. This further attests the precious value of PL as a nutraceutical in human health.

In respect to PL leaves oil, the fruits oil changes significantly its chemistry: limonene, sabinene, and myrcene have been dosed as the main representative fractions in addition to α-pinene [76]. Also, the oil from the berries is rich in anthocyanins, which confer high antioxidant ability to the material and induce autophagy, a self-degradative process that plays an important role in cell survival and maintenance [77].

5. Anti-inflammatory activity

As mentioned above among the ethnopharmaceutical indications, the anti-inflammatory effect of PL is of high importance. On this matter, many studies demonstrated the mechanisms by which PL modulates the immune-inflammatory cascade. With this purpose, the anti-inflammatory properties of the oil and extracts were tested toward the activity of pro-inflammatory cytokines, i.e. interleukin (IL)-1β, IL-6, and tumour necrosis factor-α (TNF-α). Also, the inhibitory capacity against the arachidonic acid cascade, particularly against cyclooxygenase (COXs) and lipoxygenase (LOXs) enzymes, by which derive accumulation of prostaglandins and leukotrienes, has been investigated. Furthermore, the protective effect of PL against reactive oxygen species (ROS) molecules has been largely proved. These evaluations have been conducted by means of in vitro and in vivo analysis both using the whole compounds or selective chemical fractions of PL EO or extract (Table 4).
### Table 4: Anti-inflammatory activity of *Pistacia lentiscus*

| Author (year) | Plant origin | Plant material | Main compounds | Experimental setting | Studied variable | Result |
|---------------|--------------|----------------|----------------|----------------------|------------------|--------|
| Barra et al 2007 | Sardinia, Italy | Leaves EO | α-pinene, terpinen-4-ol, p-cymene, β-myrcene, β-pinene. | ROS inhibition | DPPH as Trolox equivalent antioxidant capacity (TEAC) | 0.52 - 4.61 TEAC mmol/L |
| Benhammou et al 2008 | Algeria | Leaves extract | Flavonols, phenolic acids, flavones, anthocyanins, gallic acid, | ROS inhibition | FRAP (mg Fe²⁺/mL plant extract) | At 3 mg/mL, the reducing power was 2.86 which was very close to that of ascorbic acid (2.83) used as a control |
| Atmani et al 2009 | Algeria | Leaves extract | Not available | ROS inhibition | FRAP | At 100 μg/mL, 0.91 - 0.99% |
| Gardeli et al 2011 | Zakynthos (Greek) | Leaves extract | α-pinene, β-caryophyllene, δ-cadinene, cubebol, β-bisabolene | ROS inhibition | DPPH | IC₅₀ = 5.09 - 11.0 μg/mL |
| Maxia et al 2011 | Sardinia, Italy | Leaves EO | α-pinene, α-thujene, camphene, sabinene, β-pinene | Carrageenan-induced paw edema and cotton pellet | TNF-α, IL-6 | 1 mL/kg, significantly reduced TNF-α to 80.0% and IL-6 to |
| Study          | Location  | Plant Part | Extract Type | Compound(s)                          | Phenomenon or Assay                | Result/Findings                                                                 |
|---------------|-----------|------------|--------------|--------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Quartu et al 2012 | Sardinia, Italy | Leaves EO | Germacrene D, β-caryophyllene, α-pinene, myrcene, β-phellandrene, and α-humulene | BCCAO in rat model | DHA: no change | In Western blot the staining intensity of COX-2 band decreased significantly (p < 0.05) vs. the sham operated rat control |
| Bullitta et al 2013 | Sardinia, Italy | Leaves extract | Not available | HUVEC: more ROS after H2O2 vs control cells without H2O2 | Cytotoxicity MTT | At 50 μg/mL viability HUVEC: 50% HL-60: 80% |
|               |           |            |              | DPPH IC50 214.91±15.85 mmol TEAC/100 g DW | ROS Inhibition DPPH as mmol Trolox equivalents antioxidant capacity per 100 g dry weight | 7.3±0.32 μg/mL ABTS 201.4±5.76 mmol TEAC/100 g DW |
| Source                  | Region   | Plant Part | Constituents                  | Effect                                                                 | Concentration          | Inhibition (%)          |
|------------------------|----------|------------|-------------------------------|------------------------------------------------------------------------|------------------------|-------------------------|
| Dellai et al 2013      | Tunisia  | Leaves     | Not available                 | Carrageenan-induced paw edema in rat                                   | 50 mg/kg               | 29.8 - 63.1% and        |
|                        |          |            |                               | edema and ulcer inhibition                                             |                        | HCl/ethanol gastric ulcer by 85.3 - 95.4% |
| Remila et al 2015      | Algeria  | Fruits, leaves | Phenolic acids, flavonoids, tannins | Monocytic cell line (THP-1), Mammary tumour cells (EMT6) mouse melanoma cells (B16F10) | 100 μg/mL after 24 h, fruits extract: no cytotoxic effect, leaves extract: 83.7±1.9% | 85.3 - 95.4% |
|                        |          |            |                               | MTT                                                                    |                        | Fruits extract IC$_{50}$ = 179 μg/mL, leaves extract IC$_{50}$ = 260 μg/mL | |
|                        |          |            |                               |                                                                       |                        | B16F10: fruits extract IC$_{50}$ = 56.4 μg/mL, leaves extract IC$_{50}$ = 58.0 μg/mL | |
|                        |          |            |                               |                                                                       |                        |                         | |
| Saiah et al 2016       | Algeria  | Leaves     | Terpenes, tannins, saponins, flavonoids, alkaloids. | ROS Inhibition                                                      | DPPH                  | Inhibition by 44.0 - 95.7% |
| Piccolella et al. (2016) | Campania (Italy) | Leaves extract | Lupeol, lupenone, β—amyrin, β—sitosterol, α—tocopherol, lupanol | SH-SY5Y human neuroblastoma cells, SK-N-BE(2)C human bone marrow neuroblastoma cells | FRAP | 376.4±4.5 (mmol Fe²⁺/L plant extract) |
|-------------------------|------------------|----------------|-------------------------------------------------|------------------------------------------------------------------------------------------------|------|----------------------------------|
|                         |                  |                |                                                | Lipidperoxidation                                                                         | BCB  | At 1000 to 4000 μg/mL, 73.5±2.3% - 90.1±3.3% (% radical scavenging) |
|                         |                  |                |                                                | Intracellular ROS                                                                         |      | ROS genesis higher than 400 mM H₂O₂ by 21.3% and 93.4%, at 50 and 100 μg/mL |
|                         |                  |                |                                                | Oxidized glutathione                                                                       |      | At 100 μg/mL increase up to 170% |
|                         |                  |                |                                                | MTT                                                                                      |      | At 48 h |
|                         |                  |                |                                                | SH-SY5Y: IC₅₀ = 36.2±1.7 μg/mL                                                             |      | |
|                         |                  |                |                                                | SK-N-BE(2)C : IC₅₀ = 85.4±0.9 μg/mL                                                         |      | |
|                         |                  |                |                                                | SRB                                                                                      |      | At 48 h |
|                         |                  |                |                                                | SH-SY5Y: IC₅₀ = 29.4±0.2 μg/mL                                                             |      | |
|                         |                  |                |                                                | SK-N-BE(2)C : IC₅₀μg = 50.4±1.5 μg/mL                                                       |      | |
| Bouyahya et al. 2019    | Morocco          | Fruits EO, leaves EO | Myrcene, α-pinene, limonene, α—phellandrene, α—terpineol, γ—terpineol. | Embryonal rhabdomyosarcoma cell lines (L20B and RD), peripheral blood mono-nuclear cells (PBMC) | MTT  | L20B IC₅₀ for fruits EO: 33.0 ± 2.8 μg/mL |
|                         |                  |                |                                                | for leaves EO: 56.3±3.4 μg/mL                                                             |      | for leaves EO: 116.8±6.4 μg/mL |
|                         |                  |                |                                                | RD                                                                                       |      | |
|                         |                  |                |                                                | IC₅₀ for fruits EO: 26.4±2.1 μg/mL                                                         |      | |
|                         |                  |                |                                                | for leaves EO: 116.8±6.4 μg/mL                                                             |      | |

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doi:10.20944/preprints202102.0455.v1
IC₅₀ for fruits EO: 152.4±5.6 μg/mL
for leaves EO: 122.2 ± 2.73 μg/mL

DPPH
Fruits EO: IC₅₀ = 29.6±3.0 μg/mL
leaves EO: IC₅₀ = 38.7±6.2 μg/mL

FRAP
Fruits EO: IC₅₀ = 38.7±6.2 μg/mL
leaves EO: IC₅₀ = 65.5±4.1 μg/mL

ABTS
Fruits EO: IC₅₀ = 73.8 ± 4.0
Leaves EO: IC₅₀ = 113.72 ± 7.91 μg/mL

| Authors          | Location       | Sample Type   | Flavonoid and phenol content                                      | Cell Line                  | WST-8 Result                      |
|------------------|----------------|---------------|-----------------------------------------------------------------|----------------------------|----------------------------------|
| Mandrone et al 2019 | Sardinia, Italy | Leaves extract, fruit extract | - | African green monkey kidney cells (Vero ATCC CCL-81) | Leaves extract: CC₅₀ = > 200 μg/ml |
|                  |                |               | Flavonoid and phenol content | Human fibroblast cell lines | fruit extract: CC₅₀ = 84.2 [74.2-95.5] μg/ml |

| Milia et al 2020 | Sardinia, Italy | Leaves EO | (-)-α-pinene, terpinen-4-ol, sabinene, α-phellandrene, γ-terpinene, α-terpinene | Human fibroblast cell lines | MTT No decrease up to 100 μg/mL |
|------------------|----------------|-----------|-----------------------------------------------------------------------------|----------------------------|---------------------------------|
|                  |                | (-)-α-pinene, terpinen-4-ol, sabinene, α-phellandrene, γ-terpinene, α-terpinene | Human fibroblast cell lines |                           |                           |

ECC +550 mV corresponding to low antioxidant capacity
5.1 Inhibitory activity against proinflammatory cytokines

Remila and co-workers [78] examined the anti-inflammatory activity of leaves and fruits extract by measuring the secretion of IL-1β by macrophages exposed to adenosine triphosphate (ATP) or H₂O₂. The authors found PL leaves extract significantly reduced the production of IL-1β from ATP or H₂O₂ activated cells. The inhibitory capacity of the leaves extract was higher in comparison to that of the fruits and of quercetin and gallic acid (tested as isolated fractions of the polyphenol mixture). The data was explained in the higher content of the total phenols and flavonoids in the leaves compared to the fruits and by synergy between the pharmacological terpenes of PL extract.

The anti-inflammatory efficacy was confirmed in rats model using the carrageenan induced paw edema and cotton pellet induced granuloma [41]. Particularly, it was evidenced that when applied topically, PL EO from leaves significantly inhibited the development of granuloma and the serum level of TNF-α and IL-6 in replay to the irritants. The result was mainly related to the activity of α-pinene, β-pinene, α-phellandrene, and sabinene that were highly represented in the chemistry of that hydrodistilled oil.
5.2 Inhibitory activity against arachidonic acid cascade

Only one study has investigated the inhibitory activity of PL oil from leaves against COXs and LOXs [15]. The IC$_{50}$ values was $10.3 \pm 4.4 \mu g/mL$ and $6.1 \pm 2.5 \mu g/mL$ for COX-1 and COX-2 respectively, with higher inhibitory activity toward COX-2 in comparison to COX-1. Also, COX-2 inhibition by the EO was similar to that recorded using Ibuprofen as a positive control. The activity of the oil against LOX did not reach the IC$_{50}$ value, as PL EO lowered LOX activity by 30% compared to the control. Although the low LOX inhibition, the study strengthens the oil as a dual inhibitory potential compound, which was intensively researched in pharmacology to antagonize a great number of inflammatory processes where these enzymes sustain and amplify the disease [79, 80].

The data obtained in that investigation were addressed to the mixture of terpenoids composing the oil with particular regard to α-pinene and terpinen-4-ol (33.38%), enriched by the non-cannabinoid terpenoid limonene (3.89%), β-myrcene (0.87%), (Z)-caryophyllene (1.39%) and (E)-β-caryophyllene (0.07%). The mixture allowed to classify the oil as pharmacologically active [6].

5.3 Inhibiting activity against ROS molecules

The antioxidant potency of PL EO and extracts has been closely related to the richness in polyphenols, including tannins and flavonoids, sterols and monoterpenes [81, 82]. Also, the high content in fatty acids, such as oleic acid and linoleic acid, increases the scavenging activity [12]. The protective effects of polyphenols have been connected to the capacity to transfer electrons to free radicals and chelate metal catalysts [83], to activate antioxidant enzymes [84], to reduce α-tocopherol radicals [85] and to inhibit known free radical producing enzymes, such as myeloperoxidase and NADPH oxidase [86], and xanthine oxidase [87]. Furthermore, flavonoids have demonstrated the capacity to inhibit LDL peroxidation with important cardioprotective effects [88]. Many studies focused to demonstrate these capacities.

Remila and co-workers [78] proved the high antioxidant capacity of PL leaf extract using the oxygen radical absorbance capacity in macrophages, melanoma and mammary mouse cell lines. Furthermore, due to activation of apoptosis mechanisms, the extracts significantly inhibited the growth of melanoma cells. The data was related to the richness in phenolics, flavonoids and tannins in the extracts. Similar conclusions were obtained by Atmani [89], who examined hexane, and chloroform aqueous extracts of PL leaves by the highly concentrated flavonoids. In relation to the peak of hydroxyl groups, the aqueous formulations strongly inhibited lipid peroxidation. The mechanism was explained in the scavenging of peroxyl radicals by the extracts. Radicals play a role in development of cardiovascular disease and cancer. In this regard, it is particularly attractive the scavenger activity of gallic acid and galloylquinic derivatives, isolated from PL leaves. Notable, a progressive increase of the anti-radical activity associated with the number of galloyl groups in quinic acid was found [90]. Furthermore, all the tested metabolites strongly reduced the oxidation of low-density lipoproteins, thus strengthening the protection of PL against the lipid peroxidation.

Although having preventive capacity, a potential ability to halt or reverse oxidative stress-related diseases has been endorsed to PL. In fact, the ability in fighting aggressive tumours, *i.e.* glioblastoma and neuro-blastoma [55], and other important tumour cell lines have been proved by *in vitro* studies [91-93].

Animal testing further explored the anti-ROS efficacy of PL derives. Khedir and co-workers [94] determined the scavenger and anti-inflammatory activity of the fruits oil using the carrageenan-induced paw edema in rat model. In that study, PL oil demonstrated significant better anti-inflammatory activity with edema inhibition, in comparison to those produced by the control NADPH. Moreover, PL oil was able to increase the expression of superoxide dismutase, catalase, and glutathione peroxidase, which are released as a response to the oxidative stress in the inflamed tissue. The effects were interpreted as a consequence of the content of humulene, caryophyllene, and...
polyunsaturated fatty acid in the oil. Humulene and caryophyllene have been shown to inhibit the nuclear factor kappa B (NF-kB) pathway, responsible for the transcription of several proinflammatory cytokines, *i.e.* TNF-α, IL-1β, IL-6, and iNOS and COX-2 enzymes [95]. The polyunsaturated fatty acid in the oil might have partially replaced the arachidonic acid in the inflamed cell membranes [96], consequently lowering COX-2 production, the local inflammation and ROS generation.

Other *in vivo* studies demonstrated the administration of PL oil before the induction of the Bilateral Common Carotid Artery Occlusion followed by Reperfusion (BCCAO/R) is able to prevent the oxidative stress challenge in the nervous tissue due to the ischemic insult [13, 97]. In the cerebral tissue, PL oil restored the membrane phospholipid DHA and decreased the activity of COX-2 enzyme. Also, PL oil increased the concentration of the anti-inflammatory endocannabinoid congeners palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) [13]. The outcomes were related to the high presence of the phytocannabinoid *(E)-β*-caryophyllene, which worked synergistically with the other compounds in the oil expanding the levels of cannabinoid receptor type 2 (CB2) and PPAR-alpha receptors. Further researches attest the role of β-caryophyllene as CB2 agonists demonstrating its capacity to antagonize the release of cytokines from LPS-stimulated monocytes (TNF-α and IL-1β) [98, 99].

### 6. Antimicrobial activity

Several studies reported about the antimicrobial activity of PL terpenes. Commonly studied pathogens comprise bacteria known for antibiotic resistance (*Staphylococcus aureus* incl. *methicillin-resistant strains* (MRSA), *Escherichia coli*, *Pseudomonas aeruginosa*), bacteria associated with oral diseases as well as yeasts with particular regard to *Candida albicans* (Table 5).
| References          | Geographical origin | Test Material                  | Main components                                           | Test method¹ | Bacteria                        | Fungi                              | Origin of strain (number of strains if more than 1) | Results Agar diffusion test (mm of inhibition) | Results MIC (mg/ml) |
|---------------------|---------------------|--------------------------------|-----------------------------------------------------------|--------------|--------------------------------|-------------------------------------|---------------------------------------------------|-----------------------------------------------|---------------------|
| Iauk et al. 1996    | Sicily (Italy)      | Aerial parts ethanol extract, aerial parts water extracts (decoction) (WE) | Not available                                               | MIC          | *Staphylococcus aureus*         | *Escherichia coli*                  | ATCC 29213                                                                 | 2.5 – 0.3                  | 2.5-0.3                                       |
|                     |                     |                                |                                                           |              | STAPHYLOCOCCUS AUREUS            | ESPERICHIA COLI                     | ATCC 35218                                                                 | 2.5-0.3                        | 2.5-0.3                                       |
|                     |                     |                                |                                                           |              | CANDIDA ALBICANS                 | CANDIDA PARAPSILOSIS               | Clinical (n=18)                                                                       | 1.2-2.5 – 0.1-0.6             |                                               |
|                     |                     |                                |                                                           |              | CANDIDA GLABRATA                 | CANDIDA GLABRATA                   | Clinical (n=9)                                                                       | 0.6-1.2 - 0.1-0.3            |                                               |
|                     |                     |                                |                                                           |              | CANDIDA GLABRATA                 | CANDIDA GLABRATA                   | Clinical (n=11)                                                                       | 0.3-0.6 – 0.03-0.1           |                                               |
|                     |                     |                                |                                                           |              | CRYPTOCOCCUS NEOFORMANS          | CRYPTOCOCCUS NEOFORMANS            | Clinical (n=5)                                                                       | 1.25-2.5 – 0.3-0.6           |                                               |
| Ben Douissa et al. 2005 | Tunisia           | Leaves essential oil          | α-pinene, 4-terpinenol, β-phellandrene, sabinene, γ-terpinene, β-pinene | MIC (0.03-0.15-0.62-2.5-10.0-40.0 mg/mL) | *S. aureus* | *Enterococcus faecalis*         | *Salmonella enteritidis*              | ATCC 25923                                                                 | ≤0.03                        |                                               |
|                     |                     |                                |                                                           |              | *S. AUREUS*                      | *ENTEROCOCCUS FAECALIS*             | ATCC 29212                                                                 | 2.5                             |                                               |
|                     |                     |                                |                                                           |              | *S. AUREUS*                      | *SALMONELLA ENTERITIDIS*            | ATCC 13076                                                                 | ≤0.03                        |                                               |
| Study                | Location   | Plant Part             | Extraction Method                      | Antimicrobial Components                                                                 | Compound Concentration | Microorganisms                          | Clinical Use | MIC (mm) |
|---------------------|------------|------------------------|----------------------------------------|-----------------------------------------------------------------------------------------|------------------------|------------------------------------------|--------------|----------|
| Turchetti et al. 2005 | Tuscany (Italy) | Leaves ethyl acetate and methanol extract | Gallic acid and galloyl derivatives of both glucose and quinic acid; myricetin, quercetin glycosides; anthocyanins, catechin | ADD (100/8), MIC                                                                 |                        | *Salmonella typhimurium* NRRLB 4420 |              | 0.15     |
|                     |            |                        |                                        |                                                                                        |                        | *E. coli* ATCC 25922                    |              | 10       |
|                     |            |                        |                                        |                                                                                        |                        | *Pseudomonas aeruginosa* ATCC 27853     |              | 2.5      |
| Benhammou et al. 2008 | Algeria    | Leaves ethanol extract | Flavonols, phenolic acids, flavones, anthocyanins, gallic acid, *para*-coumaric acid | ADD (5 and 10/6mm)                                                              |                        | *S. aureus* ATCC 601                    |              | 11.5-21.5 |
|                     |            |                        |                                        |                                                                                        |                        | *Listeria monocytogenes* ATCC 19111     |              | 10-11    |
### Klebsiella pneumoniae
- **K. pneumoniae**
- **521573**
- **No inhibition**

### Pseudomonas aeruginosa
- **P. aeruginosa**
- **22212004**
- **4404540**
- **10.5-14.5**

### S. typhi
- **S. typhi**
- **0536040**
- **11-25.5**

### Proteus mirabilis
- **Proteus mirabilis**
- **054172**
- **0-14.6**

### E. coli
- **E. coli**
- **5044172**
- **No inhibition**
- **1305573**
- **0-14.6**

### Proteus mirabilis
- **Proteus mirabilis**
- **0536040**
- **9-13**

### S. aureus
- **S. aureus**
- **Not given**
- **19-30**

### Streptococcus sp.
- **Streptococcus sp.**
- **Not given**
- **0-9**

### E. coli
- **E. coli**
- **Not given**
- **9-15**

### K. pneumoniae
- **K. pneumoniae**
- **Not given**
- **17-30**

### Pseudomonas sp.
- **Pseudomonas sp.**
- **Not given**
- **0-10**

### Salmonella sp.
- **Salmonella sp.**
- **Not given**
- **9-14**

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### Aouinti et al. 2013
- **Aouinti et al. 2013**
- **Eastern Morocco**
- **Aerial parts from different areas of Morocco**
- **Taforalt and Saidia areas: limonene, α-pinene, α-terpineol and β-caryophyllene**
- **ADD (not given)**
- **Laayoune and Jerada areas: myrcene, and β-caryophyllene**

### S. aureus
- **S. aureus**
- **Not given**
- **19-30**

### Streptococcus sp.
- **Streptococcus sp.**
- **Not given**
- **0-9**

### E. coli
- **E. coli**
- **Not given**
- **9-15**

### K. pneumoniae
- **K. pneumoniae**
- **Not given**
- **17-30**

### Pseudomonas sp.
- **Pseudomonas sp.**
- **Not given**
- **0-10**

### Salmonella sp.
- **Salmonella sp.**
- **Not given**
- **9-14**

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### Mezni et al. 2014
- **Mezni et al. 2014**
- **Tunisia**
- **Fruits essential oil, phenolic extract**
- **ADD (not given)**
- **MIC**
- **S. aureus**
- **Not given**
- **0-9.33**
- **60-250**
| Species                  | Minimum | Maximum | MIC (µg/mL) |
|-------------------------|---------|---------|-------------|
| *Bacillus subtilis*     | Not given | 0       | 60-250      |
| *L. monocytogenes*      | Not given | 0-33    | 60-250      |
| *E. coli*               | Not given | 0-7     | 60-250      |
| *P. aeruginosa*         | Not given | 0       | 125-250     |
| *Aeromonas hydrophila*  | Not given | 0-7.33  | 125-250     |
| *S. typhimurium*        | Not given | 0-8     | 7-250       |
| *Aspergillus flavus*    | Not given | 0-9     | 60-250      |
| *Aspergillus niger*     | Not given | 7-9.33  | 250         |
| *C. albicans*           | Not given | 0-9     | 7-250       |

**Saiah et al. 2015**

- **Location**: Algeria
- **Extraction**: Aerial part methanol extract
- **Extract Components**: Terpenes, tannins, saponins, flavonoids, alkaloids
- **ADD**: (10/12), MIC
- **Activities**:
  - *S. aureus*: Not given, 12.2±0.42 µg/mL, 0.09 µg/mL
  - *E. coli*: Not given, 12.5±0.63 µg/mL, 0.09 µg/mL
  - *P. aeruginosa*: Not given, 13.9±1.51 µg/mL, 0.09 µg/mL

**Missoun et al. 2017**

- **Location**: Algeria
- **Extraction**: Leaves and stems methanol extract, leaves and stems aqueous extracts
- **Extract Components**: Flavonoids, alkaloids, saponins, tannins, glycosides, terpenoids, and steroids
- **ADD**: (50/5), MIC
- **Activities**:
  - *S. aureus*: Not given, 16-25 µg/mL, 50 µg/mL
  - *E. coli*: Not given, 5-7 µg/mL, 100 µg/mL

**Orru’ et al. 2017**

- **Location**: Sardinia (Italy)
- **Extraction**: Fruits essential oil
- **Extract Components**: Not showed
- **ADD**: (50/10), MIC
- **Activities**: *Bacillus clausii* Probiotic
| Organism                                      | Type          | Strain          | MIC            |
|----------------------------------------------|---------------|-----------------|----------------|
| *Staphylococcus hominis*                     | Clinical      | ATCC 6538       | No inhibition  |
| *S. aureus*                                  |               |                 |                |
| *Streptococcus pyogenes*                     | Clinical      |                 |                |
| *Streptococcus agalactiae*                   | Probiotic     | (n=2)           | No inhibition  | >500           |
| *Streptococcus salivarius*                   | Clinical      |                 |                |
| *Streptococcus mitis*                        |               |                 |                |
| *Streptococcus mutans*                       | Collection    |                 | No inhibition  | 500            |
| *Streptococcus intermedius*                  | Clinical      |                 |                |
| *C. albicans*                                |               |                 |                |
| *C. glabrata*                                | Clinical      |                 |                |
| *Candida krusei*                             |               |                 |                |

| Mandalone et al. 2019 | Sardinia, (Italy) | Fruit methanol extract, leave methanol extract, Flavonoids, polyphenols | MIC            |
|----------------------|-------------------|------------------------------------------------------------------------|----------------|

- *S. aureus* ATCC 25293
  - 26±9/ 9±8;
- *Staphylococcus epidermidis* ATCC 12,228
  - 49±15/ 7±13;
- *E. coli* ATCC 25,922
  - 77±8; 47±5;
- *K. pneumoniae* ATCC 9591
  - 42±3; 24±7
| Milia et al. 2020 | Sardinia (Italy) | Leaves essential oil (-)-α-pinene, terpinen-4-ol, sabinene, α-phellandrene, γ-terpinene, α-terpinene. |

|   | MIC | |
|---|---|---|
| *Streptococcus gordonii* ATCC 10558 | 12.5 |
| *Actinomyces naeslundii* ATCC 12104 | 3.13 |
| *Fusobacterium nucleatum* ATCC 25586 | 6.25 |
| *Porphyromonas gingivalis* ATCC 33277 | 3.13 |
| *P. gingivalis* Clinical (n=2) | 1.63 |
| *Tannerella forsythia* Laboratory | 3.13 |
| *T. forsythia* Clinical (n=2) | 1.63/3.13 |
| *C. albicans* Laboratory | 12.5 |
| *C. albicans* Clinical (n=2) | 12.5 |
| *C. glabrata* Laboratory | 6.25 |
| *C. glabrata* Clinical (n=2) | 6.25 |

1 for ADD (μl (Pistacia formulation)/mm (diameter of test disc))
Although α-pinene together with the monoterpenes terpinene and myrcene are among the most represented fractions in the Mediterranean antimicrobial oils, (Table 5), it is of general interest if higher antimicrobial activity could be related to specific PL chemotypes [100]. In this contest, as just reported regarding the anti-inflammatory capacity, synergy between chemical fractions are proposed to explain PL antimicrobial activities.

Synergy was recently claimed to discuss the inhibitory activity of the EO against *Porphyromonas gingivalis*, *Tannerella forsythia* as laboratory as clinical isolate sp. and *Fusobacterium nucleatum* [15] (Milia et al 2020). In particular, the MIC of such PL EO against *P. gingivalis*, and *T. forsythia* was 3.13 mg/mL. The result was related to the pharmacological interplay of the terpenes characterizing the oil chemotype from North Sardinia, which was α-pinene-terpinen-4-ol, further augmented by the non-cannabinoid terpenoids limonene and β-myrcene, the sesquiterpenes (Z)-caryophyllene and (E)-β-caryophyllene. Interestingly, using the MTT assay, that study also documented an increase in viability of fibroblasts in the presence of the EO, together with good biocompatibility to oral fibroblasts and keratinocytes. All these reports remark the extraordinary biological character of PL EO.

Synergy between the polyphenols composing the extracts is also claimed explaining their antimicrobial potency [24, 29, 30, 101]. This is the case of the ethanol extract of fruits, which showed the higher inhibition potential against *P. gingivalis* in comparison to other 20 extracts of pharmaceutical plants [101]. Furthermore, the potency of the fruits extract resulted higher than that of the leaves and woody parts, with MIC values against *P. gingivalis* of 8 μg/mL. Additionally, the selective index (SI) of cytotoxicity to human gingival cells was >256, meaning that all the agents have therapeutic benefit with no toxicity.

Recently, Mandrone and co-workers [102] related the antimicrobial activity of aqueous MeOH extracts of fruits and leaves to the concentration of phenolic components. That research further attests the high potential of the extracts against multi-resistant bacteria among which MRSA, and *carbapenemase-producing Klebsiella pneumoniae*.

Concerning *Candida* sp., the activity of PL derivates is reported very controversial (Table 5). Low or any sensitivity of the yeast to the leaves and or aerial parts, or to the fruits oil was often found. Despite this, PL leaves oil from Sardinian biodiversity produced low MIC values against the yeasts, ranging from 6.25 mg/mL for *C. glabrata* to 12.5 mg/mL for *C. albicans* [15]. The results were explained in a consequence of the recurrence of pharmacological concentrations of six terpenes, which were above 0.05% in the fingerprint. Also, the EO documented the ability to inhibit COX-2 and LOX, which are very important proteins to the development of *Candida* virulence.

Further high inhibition of *C. albicans* was reported using PL extracts. The activity of water or ethanol extracts has been attributed to the flavonoid contents. Noteworthy, the phenolic compound tannic acid was reported as more active against the yeast than the antifungals nystatin and amphotericin [101].

### 7. Summary and conclusion

In this review, we summarized the existing knowledge about PL phytochemistry and some of its biological activities mainly focusing to its anti-inflammatory and antimicrobial capacity.

The chemistry shows that PL EO is composed of up to 64 molecules, while till 46 constituents are present in the extracts. Further minor fractions have been indicated in the reports even if they could not be quantified. The more recurrent chemical components in the plants growing in the Mediterranean area are represented by α-pinene, terpinenes, caryophyllene, limonene, and myrcene. Important properties in antagonizing immune-mediated and autoimmunity, neuroinflammatory, neurological, and neurodegenerative diseases, in addition to infections and cancer are attributed to these molecules. Nevertheless, the biological character of PL cannot be addressed to only one of the main...
concentrated molecules. The abilities should be referred to the mixture of the whole terpenes working in synergy or in addition independently by their concentration in the agent. It is remarkable to note that concentrations of non-cannabinoid terpenoids equal or above 0.05% increase the pharmacological potency of PL oil. Regarding the extract, the high polyphenol content is attracting in prevention, and in therapy of chronic illness and infections.

Regarding the anti-inflammatory capacity, PL EO and extracts are able to inhibit the proinflammatory cytokines IL-1β, IL-6, and TNF-α. Also, it was highlighted the capacity to reverse the arachidonic acid cascade particularly antagonizing COX-2, enzyme and then the first phase of the active inflammation by the inhibition of prostaglandins. The potential LOX inhibitory capacity could propose PL as a COX-2-LOX dual inhibitory natural compound, which might have potential against inflammation and the consequent tissue damage.

Among the non-cannabinoid terpenoid fractions, (E)-β-caryophyllene has been endorsed to the anti-inflammatory activity of the oil. Interestingly, the molecule has strong affinity to CB2, where it inhibits the release of cytokines from LPS- stimulated monocytes, such as TNF-α and IL-1β expression. Furthermore, studies in experimental animals have proved the important role of (E)-β-caryophyllene in preventing ischemic/reperfusion oxidative injury when the oil was administered as a dietary assumption. In this contest, studies strengthened the adjuvant capacity of α-pinene merging in addition to caryophyllene, in PL oils by the high anti-inflammatory properties. Conversely, in addition the non-cannabinoid myrcene, caryophyllene contributed to inhibit nitric oxide production, IL-1β-induced iNOS mRNA, NF-kB and other catabolic and inflammatory mediators being of importance in rheumatoid arthritis.

The high anti-oxidant property of the extracts is impressive in the studies. Animal testing further supports the in vitro anti-ROS potency of PL with a higher efficacy in comparison to NADPHs. The ability is attributed to the richness in polyphenols, including tannins and flavonoids, sterols and monoterpenes. Notable, the aqueous formulations showed greater capacity in inhibiting lipid peroxidation compared to other extracts. The mechanism is explained in scavenging of peroxyl radicals, which suggests PL to be preventive of cardiovascular disease and cancer. In this matter, the non-cannabinoid limonene may play a relevant role in oxidative stress-related diseases by inhibiting pro-inflammatory mediator, leukocyte migration, and vascular permeability.

In regard to the antimicrobial activity, the capacity of the oil and extracts against periodontal bacteria has been documented. This evidence can justify the popular use of PL in the case of gingival bleeding and tooth ache. This ability, further ameliorated by the anti-inflammatory potency, is attractive to a possible use of the EO to antagonize gingivitis, as a primary strategy to prevent periodontitis, and a secondary preventive strategy to recurrent periodontitis after periodontal surgery. The possibility to formulate PL as a potential oral health care product or therapeutic in periodontal disease is also based on the documented biocompatibility to oral fibroblasts and keratinocytes.

Other important considerations concern the activity of PL against Candida infections. PL inhibits the growth of C. albicans and C. glabrata with low MICs. In addition, the prevention of arachidonic acid oxidation by COX-2 and LOX antagonism by PL oil is of interest as this may inhibit the development of biofilm and disseminations. Following, PL could act directly against the yeast and indirectly against its virulence, with no oral cytotoxicity.

All the above considerations can propose PL as nutraceutical and therapeutic agent by the high capacity against a wide range of diseases based on inflammation and infections.

Conflicts of Interest: The authors declare no conflict of interest.

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