

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  $\alpha$ -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- $\kappa$ B 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)

**Table 1.** Taxonomy description of Pistacia genus.

| Genus    | Group         | Species                          |
|----------|---------------|----------------------------------|
| Pistacia | Lenticella    | <i>P. mexicana</i> HBK           |
|          |               | <i>P. texana</i> Swingle         |
|          | Eu lentiscus  | <i>P. lentiscus</i> L.           |
|          |               | <i>P. saporte</i> Burbar         |
|          |               | <i>P. weinmannifolia</i> Poisson |
|          | Butmela       | <i>P. atlantica</i> Desf.        |
|          | Eu Terebintus | <i>P. chinensis</i> Bge.         |
|          |               | <i>P. khinjuk</i> Stocks         |
|          |               | <i>P. palaestina</i> Bois.       |
|          |               | <i>P. terebinthus</i> L.         |
|          |               | <i>P. vera</i> L.                |

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,  $\alpha$  -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, Fakchich 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   |
| 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 |

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 manly 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 monoterpens, 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. Terpens 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).

Table 3 Chemical profiles of *Pistacia lentiscus*

| Main components of essential oils or plant extracts                                                                                                                                             | Plant material                                              | Test Assays      | Origin              | Authors                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|------------------|---------------------|------------------------|
| <b>Essential oil</b>                                                                                                                                                                            |                                                             |                  |                     |                        |
| $\alpha$ -pinene (16.89%), terpinen-4-ol (16.49%), sabinene (7.73%), $\alpha$ -phellandrene (7.39%), $\gamma$ -terpinene (6.30%), $\beta$ -pinene (4.30%)                                       | leaves<br>essential oil                                     | GC-MS            | Sardinia<br>(Italy) | Milia et al.<br>(2020) |
| myrcene (33.46%), $\alpha$ -pinene (19.20 %), limonene (6.58%), $\alpha$ -phellandrene (4.56%), $\gamma$ -terpineol (3.73%), $\alpha$ -terpineol (3.58%)                                        | leaves<br>essential oil                                     | GC-MS            | Morocco             | Bouyahya et al. (2019) |
| $\beta$ -caryophyllene (12.8%), germacrene-D (9.6%), elemol (8.9%), $\alpha$ -terpineol (7.8%), $\gamma$ -cadinene (7.1%), bornyl acetate (6.2%)                                                | male flowers<br>essential oil                               | GC-MS            | Tunisia             | Yosr et al. (2018)     |
| $\alpha$ -limonene (28.7%), germacrene-D (23.7%), elemol (6.7%), $\beta$ -caryophyllene (6.6%), $\alpha$ -pinene (6.0%), bornyl acetate (3.7%)                                                  | female<br>flowers<br>essential oil                          | GC-MS            |                     |                        |
| $\alpha$ -limonene (18.8%), germacrene-D (13.1%), $\beta$ -caryophyllene (8.8%), $\delta$ -cadinene (8.7%), $\gamma$ -cadinene (6.2%), $\alpha$ -pinene (4.8%)                                  | leaves of<br>male plants<br>at flowering<br>essential oil   | GC-MS            |                     |                        |
| germacrene-D (20.7 %), $\delta$ -cadinene (15.6%), $\beta$ -caryophyllene (12.1 %), $\gamma$ -cadinene (6.6%), $\delta$ -cadinol (6.1%), $\alpha$ -limonene (5%)                                | leaves of<br>female plants<br>at flowering<br>essential oil | GC-MS            |                     |                        |
| $\beta$ -myrcene (75.6%), $\alpha$ -pinene (12.6%), $\alpha$ -limonene (3.2%), $\alpha$ -terpineol (1.4%), camphene (0.8%)                                                                      | ripe fruits<br>essential oil                                | GC-MS            |                     |                        |
| terpinen-4-ol (25.2%), $\alpha$ -phellandrene (11.9%), $\beta$ -phellandrene (10.2%), $\gamma$ -terpinene (10.1%), $\alpha$ -pinene (7.6%)                                                      | leaves and<br>twigs<br>essential oil                        | GC-FID,<br>GC-MS | Sardinia<br>(Italy) | Marengo et al. (2017)  |
| $\alpha$ -pinene (24.68-9.17%), 1-4 terpineol (14.89-7.12%), $\beta$ -phellandrene (11.35-4.73%), $\beta$ -pinene (8.64-1.15%), $\beta$ -mircene (9.23-0.67%), $\alpha$ -terpineol (8.41-4.92%) | leaves<br>essential oil                                     | GC-MS            | Tuscany<br>(Italy)  | Buriani et al. (2017)  |

|                                                                                                                                                                                                                                                                                                                              |                               |                             |                             |                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------|-----------------------------|---------------------------------------|
| pinene (9.9%), limonene (8.5%), terpinen 4-ol (5.1%), $\beta$ -caryophyllene (8.2%), germacrene D (11.9%), $\delta$ -cadinene (8.5%)                                                                                                                                                                                         | leaves<br>essential oil       | GC-FID,<br>GC-MS            | Tunisia                     | Aissi et al.<br>2016                  |
| $\alpha$ -pinene (13.35%), $\alpha$ -phellandrene (10.12%), $\beta$ -phellandrene (10.45%), sabinene (7.01%), germacrene-D (6.86%), $\beta$ -caryophyllene (4.58%)                                                                                                                                                           | fruits<br>essential oil       | GC-MS                       | Tunisia                     | Ben Khedir<br>et al 2016              |
| $\delta$ -germacrene (24.78%), myrcene (19.5%), $\alpha$ -cadinol (9.53%), $\gamma$ -cadinene (5.59%), trans-caryophyllene (5.03%), limonene (4.84%)                                                                                                                                                                         | fresh leaves<br>essential oil | GC-MS                       | Greece                      | Bampouli et<br>al. (2014)             |
| $\delta$ -cadinene (17.04%), $\alpha$ -amorphene (10.32%), $\delta$ -germacrene (9.01%), trans-caryophyllene (6.32%), $\alpha$ -cubebene (5.55%), naphthalene (4.13%)                                                                                                                                                        | dried leaves<br>essential oil | GC-MS                       |                             |                                       |
| Taforalt and Saidia areas: limonene, $\alpha$ -pinene, $\alpha$ -terpineol and $\beta$ -caryophyllene;<br>Laayoune and Jerada areas: myrcene, and $\beta$ -caryophyllene.                                                                                                                                                    | leaves<br>essential oil       | GC-MS                       | Eastern<br>Morocco          | Aouinti et al<br>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<br>essential oil       | GC-MS                       | Sardinia<br>(Italy)         | Quartu et al.<br>(2012)               |
| limonene (25.5–43.8%), myrcene (23.0–33.1%), $\alpha$ -pinene (20.0–34.2%) ranges shown by 17 natural populations                                                                                                                                                                                                            | leaves<br>essential oil       | GC-FID,<br>GC-MS, C-<br>NMR | Algeria                     | Mecherara-<br>Idjeri et al.<br>(2011) |
| $\alpha$ -pinene (1.9-105 $\mu\text{g g}^{-1}$ dw), $\beta$ -caryophyllene (54-198 $\mu\text{g g}^{-1}$ dw), $\delta$ -cadinene (15-186 $\mu\text{g g}^{-1}$ dw), cubebol (15-117 $\mu\text{g g}^{-1}$ dw), $\beta$ -bisabolene (22.1- 105 $\mu\text{g g}^{-1}$ dw), $\gamma$ -muurolene (29.7-67.3 $\mu\text{g g}^{-1}$ dw) | leaves<br>essential oil       | GC-MS                       | Algeria                     | Ait Saidi et<br>al. (2011)            |
| $\alpha$ -pinene, $\alpha$ -thujene, camphene, sabinene, $\beta$ -pinene, myrcene, $\alpha$ -phellandrene, $\alpha$ -terpinene, para-cymene, $\beta$ -phellandrene, trans-ocemene, $\gamma$ -terpene, terpinolene, 2-nonanone, linalool, isopentyl isovalerate, terpin-4-ol, $\alpha$ -terpinol, and others                  | leaves<br>essential oil       | GC-MS                       | Sardinia<br>(Italy)         | Maxia et al.<br>(2011)                |
| $\alpha$ -pinene (9.4-24.9 %), terpinen-4-ol (6.8-10.6%), p-cymene (0.5-7.5%), limonene (9.0-17.8%), $\gamma$ -terpinene (3.1-3.6%)                                                                                                                                                                                          | leaves<br>essential oil       | GC-MS                       | Greece                      | Gardeli et al.<br>(2011)              |
| myrcene (39.2%), limonene (10.3%), $\beta$ -gurjunene (7.8), germacrene (4.3%), $\alpha$ -pinene (2.9%), muurolene (2.9%)                                                                                                                                                                                                    | leaves<br>essential oil       | GC-FID;<br>GC-MS            | Morocco                     | Amhamdi et<br>al. (2009)              |
| $\alpha$ -pinene (14.81-22.59%), terpinen-4-ol (14.17-28.29%), $\beta$ -myrcene (0.99-18.29%), p-cymene (14.79-16.22%), sabinene (2.51-8.13%), limonene (0.93-3.76%)                                                                                                                                                         | leaves<br>essential oil       | GC-MS                       | Sardinia<br>(Italy)         | Barra et al.<br>(2007)                |
| longifolene (12.8%), $\gamma$ -cadinene (6.2%), trans- $\beta$ -terpineol (5%), $\alpha$ -acorneol (4.6%), $\gamma$ -muurolene (4.2%), $\beta$ -pinene (3.7%)                                                                                                                                                                | aerial parts<br>essential oil | GC, GC-<br>MS               | Algeria<br>(Algiers)        | Dob et al.<br>(2006)                  |
| longifolene (16.4%), trans- $\beta$ -terpineol (15.6%), terpinen-4-ol (7%), $\gamma$ -muurolene (5.7%), $\beta$ -pinene (3.3%), $\alpha$ -pinene (2.8%)                                                                                                                                                                      |                               | GC, GC-<br>MS               | Algeria<br>(Tizi-<br>Ouzou) |                                       |

|                                                                                                                                                                                                                                                                                                                                                                                    |                                   |                     |                |                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------|----------------|----------------------------|
| $\alpha$ -pinene (19%), trans- $\beta$ -terpineol (13.1%), sabinene (12.6%), $\beta$ -pinene, (6.5%), (E)- $\beta$ -ocimene (5.5%), longifolene (5.2%)                                                                                                                                                                                                                             |                                   | GC, GC-MS           | Algeria (Oran) |                            |
| $\alpha$ -pinene (63%), $\beta$ -mircene (25%), $\beta$ -pinene (3.3%), limonene (1.5%), $\beta$ -caryophyllene (0.9%), linalool (0.5%) perillene (0.5%)                                                                                                                                                                                                                           | mastic oil                        | GC-MS               | Greece         | Koutsoudaki et al. (2005)  |
| $\alpha$ -pinene (40%), $\beta$ -mircene (9%), $\beta$ -caryophyllene (5%), $\beta$ -pinene (1.5%), limonene (1%),                                                                                                                                                                                                                                                                 | mastic gum                        | GC-MS               |                |                            |
| $\alpha$ -pinene (16.8%), 4-terpinenol (11.9%), $\beta$ -phellandrene (8.9%), sabinene (5.7%), $\gamma$ -terpinene (5.5%) and $\beta$ -pinene (4.3%)                                                                                                                                                                                                                               | leaves essential oil              | GC-MS               | Tunisia        | Ben Douissa et al. (2005)  |
| terpinen-4-ol (29.9%), $\alpha$ -terpineol, (11.6%), limonene (10.6%), (Z)-3-Hex-1-enyl benzoate (6.7%), $\alpha$ -pinene (4.2%), $\beta$ -caryophyllene (3.2%)                                                                                                                                                                                                                    | leaves essential oil              | GC-MS               | Turkey         | Duru et al. (2002)         |
| myrcene (20.58%), germacrene D (13.30%), E-caryophyllene (8.33%), $\alpha$ -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               |                |                            |
| $\alpha$ -pinene (66.48%)                                                                                                                                                                                                                                                                                                                                                          | mastic oil                        | GC-MS               |                |                            |
| $\alpha$ -pinene (79%), $\beta$ -myrcene (3%)                                                                                                                                                                                                                                                                                                                                      | gum essential oil                 | GC-MS               | Spain          | Boelens and Jimenez (1991) |
| $\alpha$ -pinene (11%), $\beta$ -myrcene (19%), $\alpha$ -terpineol + terpinen-4-ol (15%)                                                                                                                                                                                                                                                                                          | leaves essential oil              | GC-MS               |                |                            |
| $\alpha$ -pinene (22%), $\beta$ -myrcene (54%)                                                                                                                                                                                                                                                                                                                                     | unripe fruit essential oil        | GC-MS               |                |                            |
| $\alpha$ -pinene (11%), $\beta$ -myrcene (19%)                                                                                                                                                                                                                                                                                                                                     | ripe fruit essential oil          | GC-MS               |                |                            |
| <b>Plant extracts</b>                                                                                                                                                                                                                                                                                                                                                              |                                   |                     |                |                            |
| 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%), $\alpha$ -pinene (38.14%), $\beta$ -pinene (9.533%), $\alpha$ -phellandrene (10.05%), D-limonene (11.91%), $\gamma$ muurolene (7.95%), camphene (3.75%) | leaves extracts                   | UHPLC-ESI-MS, GC-MS | Egypt          | El Bisbishy 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-[(2hydroxybenzoyl) amino] anilino}-4-oxobut-2-enoic acid (28.96%), $\beta$ -myrcene (11.47%), 3-                                                                                                                                                                                                                                                                              | fruit oil extract                 | GC-MS               | Tunisia        | Ammari et al 2018          |

|                                                                                                                                                                                                                                                        |                                            |                        |                |                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------|----------------|-------------------------------|
| pentadecylphenol (8.51%), p-tolyl ester (8.36%), amino formic acid (7.51%)                                                                                                                                                                             |                                            |                        |                |                               |
| phenolic composition of seed oil (concentrations not showed)                                                                                                                                                                                           | seed oil extract                           | 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%)                                                                                                                                        | oil of ripe fruits                         | GC-MS                  | Tunisia        | Mezni et al. (2014)           |
| 46 secondary metabolites, qualitative phenolics composition                                                                                                                                                                                            | deterpenated leaves extract                | LC-ESI-MS/MS           | Italy          | Pacifico et al. (2014)        |
| 46 compounds (most abundant flavonoids, phenolic acids and their derivatives)                                                                                                                                                                          | methanol leaves extracts                   | HPLC-ESI-QTOF          | Algeria        | Rodriguez-Perez et al. (2013) |
| oils, fatty acids and sterols                                                                                                                                                                                                                          | fruits during maturation extract           | GC-MS                  | Tunisia        | Trabelsi et al. (2012)        |
| cyanidin 3-O- glucoside (71%), delphinidin 3-O-glucoside and cyanidin 3- O arabinoside (28-31%)                                                                                                                                                        | berries extract                            | 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) | ethyl acetate and methanol leaves extracts | HPLC-DAD, HPLC-MS, NMR | Italy          | Romani et al. (2002)          |

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-cannabinoids terpenoids”. In PL oil, non-cannabinoid terpenoids are more likely represented by  $\alpha$ -pinene, myrcene, limonene, (E)- $\beta$ -caryophyllene and  $\gamma$ -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  $\alpha$ -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  $\alpha$ -pinene/terpinen-4-ol chemotype [9, 15]. Similarly, the Greek oil from PL leaves is  $\alpha$ -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  $\alpha$ -pinene/terpinen-4-ol; the second is terpinen-4-ol/limonene; and the third is myrcene-rich (88%) [9]. Very characteristic is the

high content of  $\delta$ -3-carene (65%) in the Egyptian oil [64], while the monoterpene terpinen-4-ol, together with  $\alpha$ -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,  $\alpha$ -pinene (65 - 86%) and  $\beta$ -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,  $\alpha$ - and  $\beta$ -caryophyllene, D-germacrene,  $\delta$ -cadinene and  $\alpha$ -cadinol,  $\beta$ -bisabolene,  $\beta$ -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 derivatives, 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  $\alpha$ -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)-1 $\beta$ , IL-6, and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ). 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 *Pistacio lentiscus*

| Author (year)        | Plant origin      | Plant material | Main compounds                                                                             | Experimental setting                             | Studied variable                                      | Result                                                                                                        |
|----------------------|-------------------|----------------|--------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Barra et al 2007     | Sardinia, Italy   | Leaves EO      | $\alpha$ -pinene, terpinen-4-ol, <i>p</i> -cymene, $\beta$ -myrcene, $\beta$ -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 Fe <sup>2+</sup> /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 |
|                      |                   |                |                                                                                            |                                                  | SASA                                                  | 14.2%                                                                                                         |
| Atmani et al 2009    | Algeria           | Leaves extract | Not available                                                                              | ROS inhibition                                   | FRAP                                                  | At 100 $\mu$ g/mL, 0.91 - 0.99%                                                                               |
|                      |                   |                |                                                                                            |                                                  | DPPH                                                  | 90% radical inhibition corresponding to IC <sub>50</sub> = 4.24 - 4.51 at 10–100 $\mu$ g/mL                   |
|                      |                   |                |                                                                                            |                                                  | H <sub>2</sub> O <sub>2</sub> scavenging activity     | At 100 $\mu$ g/mL 22.5 - 75.1% radical inhibition                                                             |
|                      |                   |                |                                                                                            |                                                  | Linoleic acid peroxidation inhibition                 | 98.8% - 99% corresponding to IC <sub>50</sub> 0.82 – 0.84 $\mu$ g/mL                                          |
| Gardeli et al 2011   | Zakynthos (Greek) | Leaves extract | $\alpha$ -pinene, $\beta$ -caryophyllene, $\delta$ -cadinene, cubebol, $\beta$ -bisabolene | ROS inhibition                                   | DPPH                                                  | IC <sub>50</sub> = 5.09 -11.0 $\mu$ g/mL                                                                      |
|                      |                   |                |                                                                                            |                                                  | FRAP                                                  | 131 mmol/L                                                                                                    |
| Maxia et al 2011     | Sardinia, Italy   | Leaves EO      | $\alpha$ -pinene, $\alpha$ -thujene, camphene, sabinene, $\beta$ -pinene                   | Carrageenan-induced paw edema and cotton pellet- | TNF- $\alpha$ , IL-6                                  | 1 mL/kg, significantly reduced TNF- $\alpha$ to 80.0% and IL-6 to                                             |

|                        |                    |                   |                                                                                                                               |                                                                                                                                            |                                                                                             |                                                                                                                                                                                                                                                                   |
|------------------------|--------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        |                    |                   |                                                                                                                               | induced<br>granuloma in rat<br>model                                                                                                       |                                                                                             | 77.8% of the control<br>group                                                                                                                                                                                                                                     |
| Quartu et al<br>2012   | Sardinia,<br>Italy | Leaves EO         | Germacrene D, $\beta$ -<br>caryophyllene, $\alpha$ -<br>pinene, myrcene, $\beta$ -<br>phellandrene, and<br>$\alpha$ -humulene | BCCAO in rat<br>model                                                                                                                      | DHA                                                                                         | DHA: no change                                                                                                                                                                                                                                                    |
|                        |                    |                   |                                                                                                                               |                                                                                                                                            | COX-2<br>(protein)                                                                          | In Western blot the<br>staining intensity of<br>COX-2 band decreased<br>significantly (p < 0.05)<br>vs. the sham operated<br>rat control                                                                                                                          |
| Bullitta<br>et al 2013 | Sardinia,<br>Italy | Leaves<br>extract | Not available                                                                                                                 | Human<br>promyelocytic<br>leukemia cell line<br>(HL-60), Primary<br>human umbilical<br>vein endothelial<br>cord blood cell<br>line (HUVEC) | intracellular<br>ROS (DCF)                                                                  | At 50 $\mu$ g/mL<br>HL-60: after H <sub>2</sub> O <sub>2</sub> no<br>difference vs. control<br>cells without H <sub>2</sub> O <sub>2</sub> .<br>HUVEC: more ROS<br>after H <sub>2</sub> O <sub>2</sub> vs. control<br>cells without H <sub>2</sub> O <sub>2</sub> |
|                        |                    |                   |                                                                                                                               | Cytotoxicity                                                                                                                               | MTT                                                                                         | At 50 $\mu$ g/mL viability<br>HUVEC: 50%<br>HL-60: 80%                                                                                                                                                                                                            |
|                        |                    |                   |                                                                                                                               | ROS Inhibition                                                                                                                             | DPPH as<br>mmol Trolox<br>equivalents<br>antioxidant<br>capacity<br>per 100 g dry<br>weight | 214.91 $\pm$ 15.85 mmol<br>TEAC/100 g DW                                                                                                                                                                                                                          |
|                        |                    |                   |                                                                                                                               |                                                                                                                                            | DPPH IC50                                                                                   | 7.3 $\pm$ 0.32 $\mu$ g/mL                                                                                                                                                                                                                                         |
|                        |                    |                   |                                                                                                                               |                                                                                                                                            | ABTS                                                                                        | 201.4 $\pm$ 5.76 mmol<br>TEAC/100 g DW                                                                                                                                                                                                                            |

|                   |         |                                 |                                                     |                                                                                        |                                                                                     |                                                                                                                                                                                                                                                                                                                                                     |
|-------------------|---------|---------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dellai et al 2013 | Tunisia | Leaves extract                  | Not available                                       | Carrageenan-induced paw edema in rat                                                   | edema and ulcera inhibition                                                         | 50 mg/kg<br>inhibited edema by 29.8 - 63.1% and<br>HCl/ethanol gastric ulcer by 85.3 - 95.4%                                                                                                                                                                                                                                                        |
| Remila et al 2015 | Algeria | Fruits extract, leaves extract, | Phenolic acids, flavonoids, tannins                 | Monocytic cell line (THP-1), Mammary tumour cells (EMT6) mouse melanoma cells (B16F10) | MTT                                                                                 | THP-1: cell viability at 100 µg/mL after 24 h, fruits extract: no cytotoxic effect, leaves extract: 83.7±1.9%<br>EMT6: at 100 µg/mL viability > 80%; fruits extract IC <sub>50</sub> = 179 µg/mL, leaves extract IC <sub>50</sub> = 260 µg/mL<br>B16F10: fruits extract IC <sub>50</sub> = 56.4 µg/mL, leaves extract IC <sub>50</sub> = 58.0 µg/mL |
|                   |         |                                 |                                                     | Monocytic cell line THP-1                                                              | Cytoprotective effect against H <sub>2</sub> O <sub>2</sub> -induced oxidant stress | THP-1: was protected dose-dependent against H <sub>2</sub> O <sub>2</sub>                                                                                                                                                                                                                                                                           |
|                   |         |                                 |                                                     |                                                                                        | ORAC<br>µmol Trolox equivalent per 100 g of extract                                 | Fruits extract: 3664±207 µmol TE/100 gE, leaves extract: 5865±406 µmol TE/100 gE                                                                                                                                                                                                                                                                    |
|                   |         |                                 |                                                     |                                                                                        | IL-1β in stimulated macrophages (by ATP)                                            | At 100 µg/mL fruit extract: no reductionl leaves extract reduction IL-1β by 55.8%                                                                                                                                                                                                                                                                   |
| Saiah et al 2016  | Algeria | Leaves extract                  | Terpenes, tannins, saponins, flavonoids, alkaloids. | ROS Inhibition                                                                         | DPPH                                                                                | Inhibition by 44.0 - 95.7%                                                                                                                                                                                                                                                                                                                          |

|                          |                   |                      |                                                                        |                                                                                                 |                             |                                                                                                                                                                                             |
|--------------------------|-------------------|----------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |                   |                      |                                                                        |                                                                                                 | FRAP                        | 376.4±4.5 (mmol Fe <sup>2+</sup> /L plant extract)                                                                                                                                          |
|                          |                   |                      |                                                                        |                                                                                                 | BCB (% radical scavenging ) | At 1000 to 4000 µg/mL, 73.5±2.3% - 90.1±3.3%                                                                                                                                                |
| Piccolella et al. (2016) | Campani a (Italy) | Leaves extract       | Lupeol, lupenone, β—amyrin, β-sitosterol, α-tocoferol, lupanol         | SH-SY5Y human neuroblastoma cells, SK-N-BE(2)C human bone marrow neuroblastoma cells            | Lipidperoxidation           | At 25, 50, 100 µg/mL equal as 400 mM H <sub>2</sub> O <sub>2</sub> , at 100 µg/mL increase to 230%                                                                                          |
|                          |                   |                      |                                                                        |                                                                                                 | Intracellular ROS           | ROS genesis higher than 400 mM H <sub>2</sub> O <sub>2</sub> 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<br>SH-SY5Y: IC <sub>50</sub> = 36.2±1.7 µg/mL<br>SK-N-BE(2)C : IC <sub>50</sub> = 85.4±0.9 µg/mL                                                                                    |
|                          |                   |                      |                                                                        |                                                                                                 | SRB                         | At 48 h<br>SH-SY5Y: IC <sub>50</sub> = 29.4±0.2 µg/mL<br>SK-N-BE(2)C : IC <sub>50</sub> µg = 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<br>IC <sub>50</sub> for fruits EO: 33.0 ± 2.8 µg/mL<br>for leaves EO: 56.3±3.4 µg/mL<br>RD<br>IC <sub>50</sub> for fruits EO: 26.4±2.1 µg/mL<br>for leaves EO: 116.8±6.4 µg/mL<br>PBMC |



COX-1; COX-2; LOX       $IC_{50} = 10.3 \pm 4.4 \mu\text{g/mL}$ ;  
                                           $6.1 \pm 2.5 \mu\text{g/mL}$ ; not  
                                          reaching the  $IC_{50}$

DPPH = 2,2-diphenyl-1-picryl-hydrazyl-hydrate assay;

FRAP= Ferric reducing activity power assay

MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

ABTS = 2,20-azinobis (3-ethyl- benzothiazoline-6-sulphonic acid) diammonium salt

WST-8 = (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H-tetrazolium, monosodium salt) assay

$IC_{50}$  = Percentage of cytotoxicity and concentration which inhibit half-cell population compared to the drug-free control

$CC_{50}$  = Concentration which inhibits of cell metabolism of 50% compared to the drug-free control

BCCAO = transient bilateral common carotid artery occlusion

DHA= docosahexaenoic acid

BCB =  $\beta$ -carotene bleaching test

ECC = Electro-chemical characterization assay

DCF = 2',7'-dichlorofluorescein diacetate

SRB = Sulforhodamine B

ORAC = Oxygen radical absorbance capacity

IL-1 $\beta$  = ,interleukin-1 $\beta$

IL-6 = interleukin-6

TNF- $\alpha$  = tumor necrosis factor- $\alpha$

nuclear factor  $\kappa$ B = NF- $\kappa$ B

COX-1 = cyclooxygenase 1

COX-2 = cyclooxygenase 2

LOX = lipoxigenase

### 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-1 $\beta$  by macrophages exposed to adenosin triphosphate (ATP) or H<sub>2</sub>O<sub>2</sub>. The authors found PL leaves extract significantly reduced the production of IL-1 $\beta$  from ATP or H<sub>2</sub>O<sub>2</sub> 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- $\alpha$  and IL-6 in replay to the irritants. The result was mainly related to the activity of  $\alpha$ -pinene,  $\beta$ -pinene,  $\alpha$ -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<sub>50</sub> values were 10.3 ± 4.4 µg/mL and 6.1 ± 2.5 µg/mL PL EO for COX-1 and COX-2 respectively, with higher inhibitory activity toward COX-2 in comparison to that produced 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<sub>50</sub> 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 leave 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 peroxy 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 derivatives. 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- $\kappa$ B) pathway, responsible for the transcription of several proinflammatory cytokines, *i.e.* TNF- $\alpha$ , IL-1 $\beta$ , 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*)- $\beta$ -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  $\beta$ -caryophyllene as CB2 agonists demonstrating its capacity to antagonize the release of cytokines from LPS-stimulated monocytes (TNF- $\alpha$  and IL-1  $\beta$ ) [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).

**Table 5.** Antimicrobial activity determined by agar diffusion test or minimal inhibitory concentration of *Pistacia lentiscus* against bacteria and fungi of medical importance.

| References              | Geografic origin | Test Material                                                             | Main components                                                                                        | Test method <sup>1</sup>                     | 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, erial parts water extracts (decoction) (WE) | Not available                                                                                          | MIC                                          |                               |                                |                                                     |                                                |                     |
|                         |                  |                                                                           |                                                                                                        |                                              | <i>Staphylococcus aureus</i>  |                                | ATCC 29213                                          |                                                | 2.5 – 0.3           |
|                         |                  |                                                                           |                                                                                                        |                                              | <i>Escherichia coli</i>       |                                | ATCC 35218                                          |                                                | 2.5-0.3             |
|                         |                  |                                                                           |                                                                                                        |                                              |                               | <i>Candida albicans</i>        | Clinical (n=18)                                     |                                                | 1.2-2.5 – 0.1-0.6   |
|                         |                  |                                                                           |                                                                                                        |                                              |                               | <i>Candida parapsilosis</i> ,  | Clinical (n=9)                                      |                                                | 0.6- 1.2 - 0,1-0.3  |
|                         |                  |                                                                           |                                                                                                        |                                              |                               | <i>Candida glabrata</i>        | Clinical (n=11)                                     |                                                | 0.3-0.6 – 0.03-0.1  |
|                         |                  |                                                                           |                                                                                                        |                                              |                               | <i>Cryptococcus neoformans</i> | Clinical (n=5)                                      |                                                | 1.25-2.5 – 0.3-0.6  |
| Ben Douissa et al. 2005 | Tunisia          | Leaves essential oil                                                      | $\alpha$ -pinene, 4-terpinenol, $\beta$ -phellandrene, sabinene , $\gamma$ -terpinene, $\beta$ -pinene | MIC (0.03- 0.15- 0.62- 2.5- 10.0- 40.0 mg/mL |                               |                                |                                                     |                                                |                     |
|                         |                  |                                                                           |                                                                                                        |                                              | <i>S. aureus</i>              |                                | ATCC 25923                                          |                                                | ≤0.03               |
|                         |                  |                                                                           |                                                                                                        |                                              | <i>Enterococcus faecalis</i>  |                                | ATCC 29212                                          |                                                | 2.5                 |
|                         |                  |                                                                           |                                                                                                        |                                              | <i>Salmonella enteritidis</i> |                                | ATCC 13076                                          |                                                | ≤0.03               |

|                       |                 |                                           |                                                                                                                              |                    |                               |            |               |               |
|-----------------------|-----------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------|------------|---------------|---------------|
| 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   | <i>Salmonella typhimurium</i> | NRRLB 4420 |               | 0.15          |
|                       |                 |                                           |                                                                                                                              |                    | <i>E. coli</i>                | ATCC 25922 |               | 10            |
|                       |                 |                                           |                                                                                                                              |                    | <i>Pseudomonas aeruginosa</i> | ATCC 27853 |               | 2.5           |
|                       |                 |                                           |                                                                                                                              |                    | <i>C. albicans</i>            | Clinical   | No inhibition | No inhibition |
|                       |                 |                                           |                                                                                                                              |                    | <i>C. glabrata</i>            | Clinical   | No inhibition | No inhibition |
| Benhammou et al. 2008 | Algeria         | Leaves ethanol extract                    | Flavonols, phenolic acids, flavones, anthocyanins, gallic acid, <i>para</i> -coumaric acid                                   | ADD (5 and 10/6mm) | <i>C. parapsilosis</i>        | Clinical   | No inhibition | No inhibition |
|                       |                 |                                           |                                                                                                                              |                    | <i>Candida tropicalis</i>     | Clinical   | No inhibition | No inhibition |
|                       |                 |                                           |                                                                                                                              |                    | <i>Candida zeylanoides</i>    | Clinical   | No inhibition | No inhibition |
|                       |                 |                                           |                                                                                                                              |                    | <i>S. aureus</i>              | ATCC 601   | 11.5-21.5     |               |
|                       |                 |                                           |                                                                                                                              |                    | <i>Listeria monocytogenes</i> | ATCC 19111 | 10-11         |               |

|                     |                 |                                                             |                                                                                                                                                                          |                      |               |        |
|---------------------|-----------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------|--------|
|                     |                 |                                                             | <i>Klebsiella pneumoniae</i>                                                                                                                                             | 5215773              | No inhibition |        |
|                     |                 |                                                             | <i>P. aeruginosa</i>                                                                                                                                                     | 22212004             | 10.5-14.5     |        |
|                     |                 |                                                             | <i>S. typhi</i>                                                                                                                                                          | 4404540              | 11- 25.5      |        |
|                     |                 |                                                             | <i>Proteus mirabilis</i>                                                                                                                                                 | 0536040              | 9-13          |        |
|                     |                 |                                                             | <i>E. coli</i>                                                                                                                                                           | 5044172              | No inhibition |        |
|                     |                 |                                                             | <i>Enterobacter cloacae</i>                                                                                                                                              | 1305573              | 0-14.6        |        |
|                     |                 |                                                             | <i>C. albicans</i>                                                                                                                                                       | 444                  | 12-23.5       |        |
| Aouinti et al. 2013 | Eastern Morocco | Aerial parts from different areas of Morocco essential oils | Taforalt and Saidia areas: limonene, $\alpha$ -pinene, $\alpha$ -terpineol and $\beta$ -caryophyllene ; Laayoune and Jerada areas: myrcene, and $\beta$ -caryophyllene . | ADD(not given)       |               |        |
|                     |                 |                                                             | <i>S. aureus</i>                                                                                                                                                         | Not given            | 19-30         |        |
|                     |                 |                                                             | <i>Streptococcus</i> sp.                                                                                                                                                 | Not given            | 0-9           |        |
|                     |                 |                                                             | <i>E. coli</i>                                                                                                                                                           | Not given            | 9-15          |        |
|                     |                 |                                                             | <i>K. pneumoniae</i>                                                                                                                                                     | Not given            | 17-30         |        |
|                     |                 |                                                             | <i>Pseudomonas</i> sp.                                                                                                                                                   | Not given            | 0-10          |        |
|                     |                 |                                                             | <i>Salmonella</i> sp.                                                                                                                                                    | Not given            | 9-14          |        |
| Mezni et al. 2014   | Tunisia         | Fruits essential oil, phenolic extract                      | Not available                                                                                                                                                            | ADD (not given), MIC |               |        |
|                     |                 |                                                             | <i>S. aureus</i>                                                                                                                                                         | Not given            | 0-9.33        | 60-250 |

|                     |                  |                                                                      |                                                                                 |                  |                             |           |           |         |
|---------------------|------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------|-----------------------------|-----------|-----------|---------|
|                     |                  |                                                                      |                                                                                 |                  | <i>Bacillus subtilis</i>    | Not given | 0         | 60-250  |
|                     |                  |                                                                      |                                                                                 |                  | <i>L. monocytogens</i>      | Not given | 0-33      | 60-250  |
|                     |                  |                                                                      |                                                                                 |                  | <i>E. coli</i>              | Not given | 0-7       | 60-250  |
|                     |                  |                                                                      |                                                                                 |                  | <i>P. aeruginosa</i>        | Not given | 0         | 125-250 |
|                     |                  |                                                                      |                                                                                 |                  | <i>Aeromonas hydrophila</i> | Not given | 0-7.33    | 125-250 |
|                     |                  |                                                                      |                                                                                 |                  | <i>S. typhimurium</i>       | Not given | 0-8       | 7-250   |
|                     |                  |                                                                      |                                                                                 |                  | <i>Aspergillus flavus</i>   | Not given | 0-9       | 60-250  |
|                     |                  |                                                                      |                                                                                 |                  | <i>Aspergillus niger</i>    | Not given | 7-9.33    | 250     |
|                     |                  |                                                                      |                                                                                 |                  | <i>C. albicans</i>          | Not given | 0-9       | 7-250   |
| Saiah et al. 2015   | Algeria          | Aerial part methanol extract                                         | Terpenes, tannins, saponins, flavonoids, alkaloids.                             | ADD (10/12), MIC | <i>S. aureus</i>            | Not given | 12.2±0.42 | 0.09    |
|                     |                  |                                                                      |                                                                                 |                  | <i>E. coli</i>              | Not given | 12.5±0.63 | 0.09    |
|                     |                  |                                                                      |                                                                                 |                  | <i>P. aeruginosa</i>        | Not given | 13.9±1.51 | 0.09    |
| Missoun et al. 2017 | Algeria          | Leaves and stems methanol extract, leaves and stems aqueous extracts | Flavonoids, alkaloids, saponins, tannins, glycosides, terpenoids, and steroids. | ADD (50/5), MIC  | <i>S. aureus</i>            | Not given | 16-25     | 50      |
|                     |                  |                                                                      |                                                                                 |                  | <i>E. coli</i>              | Not given | 5 -7      | 100     |
| Orru' et al. 2017   | Sardinia (Italy) | Fruits essential oil                                                 | Not showed                                                                      | ADD (50/10), MIC | <i>Bacillus clausii</i>     | Probiotic |           |         |

|                         |                      |                                                             |                            |     |                       |             |               |              |
|-------------------------|----------------------|-------------------------------------------------------------|----------------------------|-----|-----------------------|-------------|---------------|--------------|
|                         |                      |                                                             |                            |     | <i>Staphylococcus</i> |             |               |              |
|                         |                      |                                                             |                            |     | <i>. hominis</i>      | Clinical    |               |              |
|                         |                      |                                                             |                            |     | <i>S. aureus</i>      | ATCC 6538   | No inhibition |              |
|                         |                      |                                                             |                            |     | <i>Streptococcus</i>  |             |               |              |
|                         |                      |                                                             |                            |     | <i>pyogenes</i>       | Clinical    |               |              |
|                         |                      |                                                             |                            |     | <i>Streptococcus</i>  |             |               |              |
|                         |                      |                                                             |                            |     | <i>agalactiae</i>     | Clinical    |               |              |
|                         |                      |                                                             |                            |     | <i>Streptococcus</i>  | Probiotic   | No inhibition | >500         |
|                         |                      |                                                             |                            |     | <i>salivarius</i>     | (n=2)       |               |              |
|                         |                      |                                                             |                            |     | <i>Streptococcus</i>  | Clinical    | 12            | 30           |
|                         |                      |                                                             |                            |     | <i>mitis</i>          |             |               |              |
|                         |                      |                                                             |                            |     | <i>Streptococcus</i>  | Collection  | No inhibition | 500          |
|                         |                      |                                                             |                            |     | <i>mutans</i>         |             |               |              |
|                         |                      |                                                             |                            |     | <i>Streptococcus</i>  | Collection  | 15            | 60           |
|                         |                      |                                                             |                            |     | <i>intermedius</i>    |             |               |              |
|                         |                      |                                                             |                            |     | <i>C. albicans</i>    | Clinical    | No inhibition |              |
|                         |                      |                                                             |                            |     | <i>C. glabrata</i>    | Clinical    | No inhibition |              |
|                         |                      |                                                             |                            |     | <i>Candida krusei</i> | Clinical    | No inhibition |              |
| Mandrone<br>et al. 2019 | Sardinia,<br>(Italy) | Fruit<br>methanol<br>extract, leave<br>methanol<br>extract, | Flavonoids,<br>polyphenols | MIC |                       |             |               |              |
|                         |                      |                                                             |                            |     |                       |             |               | 26±9/ 9±8;   |
|                         |                      |                                                             |                            |     | <i>S. aureus</i>      | ATCC 25293  |               |              |
|                         |                      |                                                             |                            |     | <i>Staphylococcus</i> |             |               |              |
|                         |                      |                                                             |                            |     | <i>epidermidis</i>    | ATCC 12,228 |               | 49±15/ 7±13; |
|                         |                      |                                                             |                            |     | <i>E. coli</i>        | ATCC 25,922 |               | 77±8; 47±5;  |
|                         |                      |                                                             |                            |     | <i>K. pneumoniae</i>  | ATCC 9591   |               | 42±3; 24±7   |

|                      |                     |                         |                                                                                                                                   |                                          |                |           |
|----------------------|---------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|----------------|-----------|
| Milia et al.<br>2020 | Sardinia<br>(Italy) | Leaves<br>essential oil | (-)- $\alpha$ -pinene,<br>terpinen-4-ol,<br>sabinene, $\alpha$ -<br>phellandrene,<br>$\gamma$ -terpinene,<br>$\alpha$ -terpinene. | MIC                                      |                |           |
|                      |                     |                         |                                                                                                                                   | <i>Streptococcus<br/>gordonii</i>        | ATCC 10558     | 12.5      |
|                      |                     |                         |                                                                                                                                   | <i>Actinomyces<br/>naeslundii</i>        | ATCC 12104     | 3.13      |
|                      |                     |                         |                                                                                                                                   | <i>Fusobacterium<br/>nucleatum</i>       | ATCC 25586     | 6.25      |
|                      |                     |                         |                                                                                                                                   | <i>Porphyromona<br/>s<br/>gingivalis</i> | ATCC 33277     | 3.13      |
|                      |                     |                         |                                                                                                                                   | <i>P.gingivalis</i>                      | Clinical (n=2) | 1.63      |
|                      |                     |                         |                                                                                                                                   | <i>Tannerella<br/>forsythia</i>          | Laboratory     | 3.13      |
|                      |                     |                         |                                                                                                                                   | <i>T. forsythia</i>                      | Clinical (n=2) | 1.63/3.13 |
|                      |                     |                         |                                                                                                                                   | <i>C. albicans</i>                       | Laboratory     | 12.5      |
|                      |                     |                         |                                                                                                                                   | <i>C. albicans</i>                       | Clinical (n=2) | 12.5      |
|                      |                     |                         |                                                                                                                                   | <i>C. glabrata</i>                       | Laboratory     | 6.25      |
|                      |                     |                         |                                                                                                                                   | <i>C. glabrata</i>                       | Clinical (n=2) | 6.25      |

<sup>1</sup> for ADD ( $\mu$ l (Pistacia formulation)/mm (diameter of test disc))

Although  $\alpha$ -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  $\alpha$ -pinene-terpinen-4-ol, further augmented by the non-cannabinoid terpenoids limonene and  $\beta$ -myrcene, the sesquiterpenes (*Z*)-caryophyllene and (*E*)-  $\beta$ -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  $\mu$ g/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  $\alpha$ -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-1 $\beta$ , IL-6, and TNF- $\alpha$ . Also, it was highlighted the capacity to adverse 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)- $\beta$ -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- $\alpha$  and IL-1  $\beta$  expression. Furthermore, studies in experimental animals have proved the important role of (E)- $\beta$ -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  $\alpha$ -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-1 $\beta$ -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.

## References

1. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*; World Health Organization: Geneva, Switzerland, **2014**; ISBN 9789241564748.
2. Hidalgo E., Dominguez C. Mechanisms underlying chlorhexidine-induced cytotoxicity. *Toxicol In Vitro* **2001**, *15*, 271–276.
3. Blobaum A.L., Marnett L.J. Structural and functional basis of cyclooxygenase inhibition, *J Med Chem* **2007**, *50*, 1425–1441.
4. Langhansova L., Landa P., Kutil Z., Tauchen J., Marsik P., Rezek J., Dong L.J., Yun ZL., Vanek T. Myrica rubra leaves as a potential source of a dual 5-LOX/COX inhibitor. *Food Agric Immunol.* **2017**, *28*, 343–353.
5. Cowan M.M. Plant products as antimicrobial agents. *Clin Microbiol Rev.* **1999**, *12*, 564–582.
6. Russo E.B. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br. J. Pharmacol.* **2011**, *163*, 1344–1364.
7. Manconi M., Petretto G., D'hallewin, G., Escribanod, E., Milia E., Pinna R., Palmieri, A., Firoznejad, M., Perish, J.E., Usachh, I., Fadda A.M., Caddeo C., Manca M.L. Thymus essential oil extraction, characterization and incorporation in phospholipid vesicles for the antioxidant/antibacterial treatment of oral cavity diseases. *Colloids Surf. B Biointerfaces* **2018**, *171*, 115–122.
8. Pinna R., Filigheddu, E., Juliano C., Palmieri A., Manconi M., D'hallewin, G., Petretto G., Maioli M., Caddeo C., Manca M.L. Solinas G., Bortone A., Campanella V., Milia E. Antimicrobial effect of Thymus capitatus and Citrus limon var. pompia as raw extracts and nanovesicles. *Pharmaceutics* **2019**, *11*, 234.
9. Barra A., Coroneo V., Dessì S., Cabras P., Angioni A. Characterization of the volatile constituents in the essential oil of Pistacia lentiscus L. from different origins and its antifungal and antioxidant activity. *J Agric Food Chem.* **2007**, *22*, 7093–7098.
10. Dimas K.S., Panayotis Pantazis P., Ramaujam R. Chios Mastic Gum: A Plant-produced Resin Exhibiting Numerous Diverse Pharmaceutical and Biomedical Properties *in vivo* **2012**, *26*, 777–786.
11. Pachi V.K., Mikropoulou, E.V., Gkiouvetidis P., Siafakas, K., Argyropoulou, A., Angelis A., Mitakou S., Halabalaki M. Traditional uses, phytochemistry and pharmacology of Chios mastic gum (Pistacia lentiscus var. Chia, Anacardiaceae): A review. *J Ethnopharmacol* **2020**, *254*, 112–485.
12. Orrù G., Demontis, C., Mameli, A., Tuveri, E., Coni, P., Pichiri, G., Coghe, F., Rosa, A., Rossi P., D'hallewin, G. The selective interaction of Pistacia lentiscus Oil vs. human Streptococci, an old functional food revisited with new tools. *Front. Microbiol.* **2017**, *8*, 20–17.
13. Quartu M., Serra M.P., Boi M., Pillolla G., Melis T., Poddighe L., Del Fiacco M., Falconieri D., Carta G. Murru E., Cordeddu L., Piras A., Collu M., Banni S. Effect of acute administration of Pistacia lentiscus L. essential oil on rat cerebral cortex following transient bilateral common carotid artery occlusion. *Lipids Health Dis* **2012**, *11*, 8.
14. Piccolella S., Nocera P., Carillo P., Woodrow P., Greco V., Manti L., Fiorentino A., Pacifico S. An apolar Pistacia lentiscus L. leaf extract: GC-MS metabolic profiling and evaluation of cytotoxicity and apoptosis inducing effects on SH-SY5Y and SK-N-BE(2)C cell lines. *Food and Chemical Toxicology* **2016**, *95*, 64–74.
15. Milia E., Usai M., Sztórková B., Elstnerová M., Králová V., D'hallewin G., Spissu Y., Barberis A., Marchetti M., Bortone A., Campanella V., Mastandrea G., Langhansová L., Sigrun E. The pharmaceutical ability of Pistacia lentiscus L. leaves essential oil against periodontal bacteria and Candida sp. and its anti-inflammatory potential. *Antibiotics* **2020**, *9*, 281.
16. Zohary M. A mono-graphical study of the genus Pistacia. *Palestine J Bot. Jerusalem Series*, **1952**, *5*, 187–228.
17. Rauf A., Patel S., Uddin G., Siddiqui B.S., Ahmade B., Muhammad N., Mabkhot Y.N., Ben Hadda T. Phytochemical, ethnomedicinal uses and pharmacological profile of genus Pistacia. *Biomed. & Pharmacother.* **2017**, *86*, 393–404.
18. Treitler J.T., Drissen T., Stadtmann R., Zerbe S., Mantilla-Contreras J. Complementing endozoochorous seed dispersal patterns by donkeys and goats in a semi-natural island ecosystem. *BMC Ecol.* **2017**, *17*, 42.
19. Rostás M., Maag D., Ikegami M., Inbar M. Gall volatiles defend aphids against a browsing mammal. *BMC Evol. Biol.* **2013**, *13*, 193.
20. Inbar M., Wink M., Wool D. The evolution of host plant manipulation by insects: molecular and ecological evidence from gall-forming aphids on Pistacia. *Mol Phylogenet Evol.* **2004**, *32*, 504–511.
21. Rand K., Bar E., Ben-Ari M., Lewinsohn E., Inbar M. The mono and sesquiterpene content of aphid-induced galls on Pistacia palaestina is not a simple reflection of their composition in intact leaves. *J. Chem. Ecol.* **2014**, *40*, 632–642.
22. Di Rosa, A. *Erbe e Pianta Medicinali in Sardegna*, 3rd ed.; Carlo Delfino Ed.: Sassari, Italy, 2018.
23. Mastino A. La produzione ed il commercio dell'olio in Sardegna. In Mario Atzori e Antonio Vodret Olio sacro e profano: tradizioni olearie in Sardegna e Corsica. Sassari, EDES Ed Democratica Sarda, 1995.
24. Elgubbi H., Alfageih L., Zorab A., Elmeheshi F. Pistacia lentiscus tree and its role in riddance of some environmental pollutants. *EC Nutrition* **2018**, *8*, 14.
25. Cabiddu A., Delgadillo-Puga C., Decandia M., Molle G. Extensive ruminant production systems and milk quality with emphasis on unsaturated fatty acids, volatile compounds, antioxidant protection degree and phenol content. *Animals* **2019**, *9*, 771.
26. Lev E. Ethno-diversity within current ethno-pharmacology as part of Israeli traditional medicine – A review. *J. Ethnobiol. Ethnomedicine* **2006**, *2*, 4.
27. Lev E., Amar Z., Ethnopharmacological survey of traditional drugs sold in the Kingdom of Jordan. *J. of Ethnopharmacol.* **2002**, *82*, 131–145.
28. Janakat S., H. Al-Merie, Evaluation of hepatoprotective effect of Pistacia lentiscus, Phillyrea latifolia and Nicotiana glauca. *J. Ethnopharmacol.* **2002**, *83*, 135–138.

29. Saiah H., Rachida Allem R., Zohra El Kebir F. Antioxidant and antibacterial activities of six Algerian medicinal plants *International J Pharm Sci* **2016**, 8, 201.
30. Missoun F., Bouabedelli F., Benhamimed E., Baghdad A., Djebli N. Phytochemical study and antibacterial activity of different extracts of *Pistacia lentiscus* L collected from Dahra Region West of Algeria. *J Fundam Appl Sci* **2017**, 9, 669-684.
31. Trabelsi H., Cherif O.A., Sakouhi F., Villeneuve P., Renaud J., Barouh N., Boukhchina S., Mayer P. Total lipid content, fatty acids and 4-desmethylsterols accumulation in developing fruit of *Pistacia lentiscus* L. growing wild in Tunisia. *Food Chemistry*, **2012**, 131, 434–440.
32. Jamila F., Mostafa E., Ethnobotanical survey of medicinal plants used by people in Oriental Morocco to manage various ailments. *J Ethnopharmacol* **2014**, 154, 76-87.
33. Giner-Larza E. M., Maez S., Recio M. C., Giner R.M., Prieto J.M., Cerdá-Nicolás M, Ríos JL. Oleanonic acid, a 3-oxotriterpene from *Pistacia*, inhibits leukotriene synthesis and has anti-inflammatory activity. *Eur. J. Pharmacol.* **2001**, 428, 137–143.
34. Rahimi R., Mozaffari S., Abdollahi M. On the use of herbal medicines in management of inflammatory bowel diseases: a systematic review of animal and human studies. *Dis. Sci.* **2009**, 54, 471–480.
35. Farzaei M. H., Rahimi R., Abbasabadi Z., Abdollahi M. An evidence-based review on medicinal plants used for the treatment of peptic ulcer in traditional Iranian medicine, *International Journal of Pharmacology* **2013**, 9, 108–124.
36. Leporatti M. L., Kamel G. Comparative analysis of medicinal plants used in traditional medicine in Italy and Tunisia. *J. Ethnobiol. Ethnomedicine* **2009**, 5-31.
37. Ballero M., F. Poli, G. Sacchetti, M.C. Loi. Ethnobotanical research in the territory of Fluminimaggiore (south-western Sardinia). *Fitoterapia* **2001**, 72, 788-801.
38. Loi M.C., Frajus L., Maxia A. Le Piante Utilizzate Nella Medicina Popolare Nel Territorio Di Gesturi (Sardegna Centro-Meridionale). *Atti Soc. tosc. Sci. flat., Mem.* **2002**, 109, 167-176.
39. Palmese M. T., Uncini Manganell R.E., Tomei P.E., An ethno-pharmacobotanical survey in the Sarrabus district (South-East Sardinia). *Fitoterapia* **2001**, 72, 619–643.
40. Atzei A. D., O.F.M Le piante della tradizione popolare della Sardegna. Carlo Delfino Eds; *IBS.it La Feltrinelli, Milano*, Italy, 2018, pp. XXIV-597.
41. Maxia A., Lancioni M.C., Balia A.N., Alborghetti R., Pieroni A., Loi M.C.. Medical ethnobotany of the Tabarkins, a Northern Italian (Ligurian) minority in south-western Sardinia. *Genet Resour Crop Evol* **2008**, 55, 911–924.
42. Leonti M., O.Staub P., Cabras S., Castellano M. E., Casu L. From cumulative cultural transmission to evidence-based medicine: evolution of medicinal plant knowledge in Southern Italy. *Front. Pharmacol.* **2015**, 6.
43. Camarda I. Ricerche etnobotaniche nel comune di Dorgali (Sardegna centro-orientale). *Bollettino della Società sarda di scienze naturali* **1989-90**, 27, 147-204.
44. Sanna C., Ballero M., Maxia A. Le Piante Medicinali Utilizzate Contro Le Patologie Epidermiche In Ogliastra (Sardegna Centro-Orientale). *Atti Soc. Tosc. Sci. nat., Mem.*, **2006**, 113, 73-82.
45. Scherrer A. M., Motti R., Caroline S. Weckerle Traditional plant use in the areas of Monte Vesole and Ascea, Cilento National Park (Campania, Southern Italy). *J. Ethnopharmacol.* **2005**, 97, 129–143
46. Gras A., Serrasolses G., Vallès J., Garnatje T. Traditional knowledge in semi-rural close to industrial areas: ethnobotanical studies in western Gironès (Catalonia, Iberian Peninsula). *J. of Ethnobiol. Ethnomedicine* **2019**, 19, 15-19.
47. Falk A. A., Hagberg M. T., Lof A. E., Wigaeus-Hjelm E. M., Wang, Z. P. Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scand. J. Work, Environ. Health*, **1990**, 16, 372–378.
48. Falk-Filipsson A., Lof A., Hagberg M., Hjelm E. W., Wang, Z. (1993). d-limonene exposure to humans by inhalation: Uptake, distribution, elimination, and effects on the pulmonary function. *Journal of Toxicology and Environmental Health*, **1993**, 38, 77–88.
49. de Cássia da Silveira e Sá R., Nalone Andrade L., Pergentino de Sousa D. A Review on Anti-Inflammatory Activity of Monoterpenes. *Molecules* **2013**, 18, 1227-1254.
50. Rufino A. T., Ribeiro M., Sousa C., Judas F., Salgueiro L., Cavaleiro C., Ferreira Mendes A. Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis. *Eur. J. Pharmacol.* **2015**, 750, 141–150.
51. Russo E.B., Marcu J. Cannabis Pharmacology: The usual suspects and a few promising leads. *Adva. in Pharmacol.*, **2017**, 80.
52. Miguel M. G. Antioxidant and anti-inflammatory activities of essential oils: a short review. *Molecules* **2010**, 15, 9252-9287.
53. Ammari M., Othmana H., Hajric A., Mohsen S., Abdelmelek H. *Pistacia lentiscus* oil attenuates memory dysfunction and decreases levels of biomarkers of oxidative stress induced by lipopolysaccharide in rats. *Brain Res. Bull.* **2018**, 140, 140–147.
54. Poddighe L., Carta G., Serra M.P., Melis T., Boi M., Lisai S., Murru E., Muredda L., Collu M., Banni S., Quartu M., Acute administration of beta-caryophyllene prevents endocannabinoid system activation during transient common carotid artery occlusion and reperfusion. *Lipids Health Dis* **2018**, 17-23 .
55. Aydin E., Türkez H., Geyikog'lu, F. Antioxidative, anticancer and genotoxic properties of a-pinene on N2a neuroblastoma cells. *Biologia* **2013**, 68, 1004-1009.
56. Piluzza G., Viridis S., Serrallutzu F., Bullitta S. Uses of plants, animal and mineral substances in Mediterranean ethno-veterinary practices for the care of small ruminants. *J Ethnopharmacol.* **2015**, 168, 87–99.
57. Benítez G., González-Tejero M.R., Molero-Mesa J. Knowledge of ethnoveterinary medicine in the Province of Granada, Andalusia, Spain. *J. Ethnopharmacol* **2012**, 139, 429–439.

58. Trindade de Santana Souza M., Guedes da Silva Almeida J.R., De Souza Araujo A.A., Cavalcante Duarte M., Pens Gelain D., Fonseca Moreira J.C., Viana dos Santos M.R., Quintans-Junior L. J. Structure–activity relationship of terpenes with anti-Inflammatory profile-a systematic review. *Basic Clin. Pharmacol. Toxicol.* **2014**, *115*, 244–256.
59. Christianson D. W. Structural and chemical biology of terpenoid cyclases. *Chem. Rev.* **2017**, *117*, 11570–11648.
60. Franz C., Novak J. Sources of essential oils. In Handbook of essential oils: Science, technology, and applications, 2nd ed.; K. H. C. Baser & G. Buchbauer Eds; Publisher: CPR Press Taylor & Francis Group, USA, Boca Raton, 2010; pp. 39–82.
61. Tassou C.C., Chorianopoulos N.G., Skandamis P.N., Nychas G.J.E. Herbs, spices and their active components as natural antimicrobials in foods. In Handbook of Herbs and Spices: . Woodhead Publishing Series in Food Science, Technology and Nutrition; K. V. Peter Eds; Publisher: Woodhead Publishing, UK, Cambridge, 2012, Volume 2, pp 17-50.
62. Farmacopea Ufficiale della Repubblica Italiana, 12th ed.; Istituto Poligrafico e Zecca dello Stato: Roma, Italy, 2008.
63. Chrysavgi G., Papageorgiou V., Mallouchos A., Kibouris T., Komaitis M. Essential oil composition of *Pistacia lentiscus* L. and *Myrtus communis* L. : Evaluation of antioxidant capacity of methanolic extracts. *Food Chem* **2008**, *107*, 1120–1130.
64. De Pooter H.L., Schamp N.M., Aboutabl E.A., Tohamy S.F., Doss S.L., Essential oil of the leaves of three *Pistacia* species grown in Egypt. *Flav. Fragr. J.* **1991**, *6*, 229-232.
65. Boelens M.H., Jemenez R. Chemical composition of the essential oil from the gum and various parts of *Pistacia lentiscus* L. (Mastic Gum Tree). *Flav. Fragr. J.* **1991**, *6*, 271-275.
66. Duru M. E., Cakir A., Kordali S., Zengin H., Harmandar M., Izumi S., Hirata T. Chemical composition and antifungal properties of essential oils of three *Pistacia* species. *Fitoterapia* **2003**, *74*, 170-176.
67. Zrira S., Elamarani A., Benjilali B. Chemical composition of the essential oil of *Pistacia lentiscus* L. from Morocco-a seasonal variation. *Flav. Fragr. J.* **2003**, *18*, 475-480.
68. Assimopoulou A.N., Zlatanov S.N., Papageorgiou V.P. Antioxidant activity of natural resins and bioactive triterpenes in oil substrates. *Food Chem.* **2005**, *92*, 721-727.
69. Romani A., Pinelli P., Galardi C., Mulinacci N., Tattini M. Identification and quantification of galloyl derivatives, flavonoid glycosides and anthocyanins in leaves of *Pistacia lentiscus* L. *Phytochem. Anal.* **2002**, *13*, 79–86.
70. Jiang F., Chen W., Yi K., Wu Z., Si Y., Han W., Zhao Y.. The evaluation of catechins that contain a galloyl moiety as potential HIV-1 integrase inhibitors. *Clin. Immunol.* **2010**, *137*, 347–356.
71. Zhao Y., Jiang F., Liu P., Chen W., Yi K. Catechins containing a galloyl moiety as potential anti-HIV-1 compounds. *Drug Discov. Today* **2012**, *17*(11-12),630-5.
72. Zhou Y., Zheng J., Li Y., Dong-Ping X., Sha L., Yu-Ming C., Hua-Bin L. Natural polyphenols for prevention and treatment of cancer. *Nutrients* **2016**, *8*, 5-15.
73. Griffiths K., Aggarwal B.B., Singh R.B., Buttar H.S., Wilson D., De Meester F. Food antioxidants and their anti-inflammatory properties: a potential role in cardiovascular diseases and cancer prevention. *Diseases* **2016** *4*, 28.
74. Min J., Mingliang Z., Wang L., Shuwen Y., Anti-tumor effects and associated molecular mechanisms of myricetin. *Biomed. Pharmacother* **2019**, *120*, 109-506.
75. Rodríguez-Pérez C., Quirantes-Pinéa R., Amessis-Ouchemouk N., Madanic K., Segura-Carretero A., Fernández-Gutiérrez A. A metabolite-profiling approach allows the identification of new compounds from *Pistacia lentiscus* leaves. *J Pharmaceut Biomed* **2013**, *77*, 167–174.
76. Bozorgi M. U., Memariani Z., Mobli M., Salehi Surmaghi M H., Shams-Ardekani M.R., Rahimi R. Five *Pistacia* species (*P. vera*, *P. atlantica*, *P. terebinthus*, *P. khinjuk*, and *P. lentiscus*): a review of their traditional uses, phytochemistry, and pharmacology. *Sci. World J.* **2013**, Article ID 219815, 33 pages.
77. Vogelmann T.C. 1993. Plant tissue optics. *A Rev Plant Physiol Plant Mol Biol* **1993**, *44*, 231-251.
78. Remila S., Atmani-Kilani D., Delemasure S., Connat J.L., Azib L., Richard T., Atmani D. Antioxidant, cytoprotective, anti-inflammatory and anticancer activities of *Pistacia lentiscus* (Anacardiaceae) leaf and fruit extracts. *Eur. J. Integr. Med* **2015**, *7*, 274–286.
79. Zhou Y., Wang G., Li Y., Liu Y., Song Y., Zheng W., Zhang N., Hu X., Yan S., Jia J. In vitro interactions between aspirin and amphotericin B against planktonic cells and biofilm cells of *Candida albicans* and *C. parapsilosis*. *Antimicrob. Agents Chemother.* **2012**, *56*, 3250-3260.
80. Liu X., Wang D., Yu C., Li T., Liu J., Sun S. Potential antifungal targets against a *Candida* biofilm based on an enzyme in the arachidonic acid cascade—A review. *Front Microbiol* **2016**, *7*, 19-25.
81. Lee J.C., Lee K.Y., Kim J., Na C.S., Jung N.C., Chung G.H., Jang Y.S. Extract from *Rhus verniciflua* stokes is capable of inhibiting the growth of human lymphoma cells. *Food Chem Toxicol* **2004**, *42*, 1383–1388.
82. Rao Y.K., Paiva L.A., Souza M.F., Campos A.R., Ribeiro R.A., Brito G.A., Teixeira M.J., Silveira E.R., Ternatin, an anti-inflammatory flavonoid, inhibits thioglycolate-elicited rat peritoneal neutrophil accumulation and LPS-activated nitric oxide production in murine macrophages. *Planta.Med.* **2003**, *69*, 851–853.
83. Ferrali, M., Signorinis C., Caciotti B., Sugherini L., Ciccoli L., Giachetti D., Comporti M. Protection against oxidative damage of erythrocyte membranes by the flavonoid quercetin and its relation to ion chelating activity. *FEBS Letters* **1997** *416*, 123–129.
84. Elliot A. J., Scheiber S. A., Thomas C., Pardini R. S. Inhibition of glutathione reductase by flavonoids. *Biochem. and Pharmacol* **1992** *44*, 1603–1608.
85. Hancock J., Desikan R., Neill S. Role of reactive oxygen species in cell signaling pathways. *Biochemical and Biomedical Aspects of Oxidase Modification* **2001** *29*, 345–350.

86. Middleton E., Kandaswami C. Effects of flavonoids on immune and inflammatory cell functions. *Biochem and Pharmacol* **1992** 43, 1167–1179.
87. Nagao A., Seki M., Kobayashi H. Inhibition of xanthine oxidase by flavonoids. *Biosci, Biotechnol and Biochem* **1999**, 63, 1787–1790.
88. Mazur A., Bayle D., Lab C., Rock E., Rayssiguier Y. Inhibitory effect of procyanidin-rich extracts on LDL oxidation in vitro. *Atherosclerosis* **1999**, 145, 421–422.
89. Atmani D., Chaheer N., Berboucha M., Ayouni K., Lounis H., Boudaoud H., Debbache N., Atman D. Antioxidant capacity and phenol content of selected Algerian medicinal plants. *Food Chem* **2009** 112, 303–309.
90. Baratto M.C., Tattini M., Galardi C., Pinelli P., Romani A., Visioli F., Basosi R., Pogni R. Antioxidant activity of galloyl quinic derivatives isolated from *P. lentiscus* leaves. *Free Radic. Res.* **2003**, 37, 405–412.
91. Bullitta S., Piluzza G., Manunta M.D.I. Cell-based and chemical assays of the ability to modulate the production of intracellular reactive oxygen species of eleven Mediterranean plant species related to ethnobotanic traditions. *Genet. Resour. Crop. Evol.* **2013**, 60, 403–412.
92. Catalani S., Palma F., Battistelli S., Benedetti S., Oxidative stress and apoptosis induction in human thyroid carcinoma cells exposed to the essential oil from *Pistacia lentiscus* aerial parts. PLOS ONE DOI:10.1371/journal.pone.0172138 February 14, 2017
93. Cappadone C., Mandrone M., Chiochio I., Sanna C., Malucelli E., Bassi V., Picone G., Poli F. Antitumor Potential and Phytochemical Profile of Plants from Sardinia (Italy), a Hotspot for Biodiversity in the Mediterranean Basin. *Plants* **2020**, 9, 26.
94. Khedir S.B., Mzid M., Bardaa S., Moalla D., Sahnoun Z., Rebai T. In vivo evaluation of the anti-inflammatory effect of *Pistacia lentiscus* fruit oil and its effects on oxidative stress. *Evid.-Based Complementary Altern. Med*, Vol.2016, Article ID 6108203,
95. Janssen-Heininger Y.M.W., Poynter M.E., Baeuerle P.A. Recent advances towards understanding redox mechanisms in the activation of nuclear factor  $\kappa$ B. *Free Radic. Biol. Med.* **2000**, 28, 1317–1327.
96. Calder P. C. Polyunsaturated fatty acids and inflammation. *Prostaglandins Leukot Essent Fatty Acids* **2006**, 75, 197–202.
97. Quartu M., Poddighe L., Melis T., Serra M.P., Boi M., Lisai S., Carta G., Murru E., Muredda L., Collu M., Banni S. Involvement of the endocannabinoid system in the physiological response to transient common carotid artery occlusion and reperfusion. *Lipids Health Dis* **2017**, 16–14.
98. Gertsch J., Leonti M., Raduner S., Racz I., Chen J.Z., Xie X.Q. Altmann, K.H.; Karsak, M.; Zimmer, A. Beta-caryophyllene is a dietary cannabinoid. *Proc. Natl. Acad. Sci* **2008**, 105, 9099–9104.
99. Gonçalves E. C. D., Baldasso M.G., Maira A., Bicca Rodrigo S., Capasso R., Dutra R. C. Terpenoids, cannabinimetic ligands, beyond the Cannabis Plant. *Molecules* **2020**, 25, 15–67.
100. Djenane D., Yanguela J., Montañés L., Djerbal M., Roncalés P. Antimicrobial activity of *Pistacia lentiscus* and *Satureja montana* essential oils against *Listeria monocytogenes* CECT 935 using laboratory media: Efficacy and synergistic potential in minced beef. *Food Control* **2011**, 22, 1046–1053.
101. Carrol D.H., Chassagne F., Dettweiler M., Quave C.L. Antibacterial activity of plant species used for oral health against *Porphyromonas gingivalis*. PLOS ONE | <https://doi.org/10.1371/journal.pone.0239316> **2020**.
102. Mandrone M., Bonvicini F., Lianza M., Sanna C., Maxia A., Gentilomi G.A., Poli F. Sardinian plants with antimicrobial potential. Biological screening with multivariate data treatment of thirty-six extracts. *Ind. Crop. Prod.* **2019**, 137, 557–565.
103. Benhammou N., Bekkara F.A., Kadifkova Panovska T. Antioxidant and antimicrobial activities of the *Pistacia lentiscus* and *Pistacia atlantica* extracts. *Afr. J. Pharm. Pharmacol.* **2008**, 2, 22–28.
104. Mezni F., Aouadhib C., Khoujaa M.L., Khaldia A., Maaroufi A. In vitro antimicrobial activity of *Pistacia lentiscus* L. edible oil and phenolic extract. *Nat. Prod. Res.* **2015**, 29, 565–70.