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Titled

**Medicinal, biological and pharmacological
aspects of *Pistacia lentiscus* L.**

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Dedication

I dedicate my work to my family and beloved wife. A feeling of gratitude to my father and mother, my Three sisters Malek, maimana and marwa in particular you have been my loving and supporting family. My wife Hadjer who have never left my side and whose words of encouragement and push for tenacity ring in my ears. I will always appreciate all they have done. I would like to extend thanks to my friend Sergey for helping me develop my scientific skills and for being a good hearted friend, and for the many hours of proofreading and academic aid, and. Anew I give special thanks to my beloved wife you have been my best cheerleader and support. Mohammed Bilal

To all my family members whose support has been decisive in the fulfillment of this thesis I dedicate this work. My parents: thank you for your love and endless support. My grandmother: thank you my blessings. My sister: I always appreciate your advice and care. A special dedication goes to my colleagues and friends who have been supportive and cooperative. Khawla

I would like to dedicate this humble work in the first respect to my grandfather's spirit. "May Allah overwhelm him with his forgiveness and mercy"

My dedication goes also to all my family members who have been of a great back and assistance all through the way. Aicha

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يهتم مجال الكيمياء النباتية باستخدام النباتات لاكتشاف علاجات جديدة ضد الأمراض والمشاكل الصحية من خلال إثبات خصائصها العلمية *Pistacia lentiscus*. هو نبات طبي وعطري ينتمي لعائلة *Anacardiaceae*. يتوزع بشكل رئيسي في منطقة حوض البحر الأبيض المتوسط. يستخدم هذا النبات بكثرة في الطب التقليدي لعلاج بعض الأمراض مثل مشاكل الجهاز التنفسي والهضمي، ارتفاع ضغط الدم، الإكزيما، الحروق ... إلخ. أثبتت البحوث والنتائج العلمية عن الأنشطة الدوائية الواسعة لأجزاء هذا النبات مثل مضادات الأكسدة، الإنهائيات، الميكروبات، الفيروسات، الجراثيم، مضادات السرطان ومضادات داء السكري ... إلخ. إضافة إلى كل هذا تم استخراج العديد من المكونات الكيميائية النباتية مثل المركبات الفينولية، التربينويدات، الأحماض الدهنية والستيرويدات من أجزاء مختلفة من نوع النبات منذ القدم حتى اليوم. تهدف الدراسة المقدمة إلى تجميع المصادر والمعلومات المتعلقة بالكيمياء النباتية والخواص الكيميائية الحيوية والدوائية والاستخدامات الطبية التقليدية لنبات الفستق العدسي *P. lentiscus*.

الكلمات المفتاحية: *Pistacia lentiscus*; الكيمياء النباتية، السمية، الطب التقليدي، الخصائص البيولوجية والدوائية.

Abstract

The field of phytochemistry is focused on the use of plants to find new treatments for health problems by proving their scientific properties. *Pistacia lentiscus* is a medicinal and aromatic plant of the Anacardiaceae family, it's found mainly in the Mediterranean basin. *P. lentiscus* is widely used in traditional medicine to treat several diseases. Such as respiratory and digestive issues, high blood pressure, eczema, burns, etc. Scientific research and findings of studies have proven the numerous pharmacological activities of parts of this plant such as antioxidant, anti-inflammatory, antimicrobial (antiviral and antibacterial antidiabetic, protective liver and anticancer effects. In addition, many bioactive phytochemical compounds such as phenolics, terpenoids, fatty acids and steroids have been extracted from different parts of *Pistacia* species, from ancient to present times. The presented study aims to compile sources and informations related to the phytochemistry, biochemical and pharmacological properties and traditional medicinal uses of *P. lentiscus*.

Key words: *Pistacia lentiscus*, phytochemistry, toxicity, traditional medicine, biological and pharmacological activities.

Résumé

Le domaine de la phytochimie est axé sur l'utilisation des plantes pour trouver de nouveaux traitements pour les problèmes de santé en prouvant leurs propriétés scientifiques. *Pistacia Lentiscus* est une plante médicinale et aromatique de la famille des Anacardiaceae, présente principalement dans le bassin méditerranéen et largement utilisée en médecine traditionnelle. Elle est utilisée pour traiter plusieurs maladies telles que les troubles respiratoires et digestifs, l'hypertension artérielle, l'eczéma, les brûlures, etc. La recherche scientifique et les résultats des études ont prouvé les nombreuses activités pharmacologiques des parties de cette plante, telles que les effets antioxydants, anti-inflammatoires, antimicrobiens, antiviraux et antibactériens, antidiabétiques, protecteurs du foie et anticancéreux. En outre, de nombreux composés phytochimiques bioactifs tels que les composés phénoliques, les terpénoïdes, les acides gras et les stéroïdes ont été extraits de différentes parties de l'espèce *Pistacia*, depuis l'antiquité jusqu'à nos jours. La présente étude vise à compiler les sources et les informations relatives à la phytochimie, aux propriétés biochimiques, pharmacologiques et aux utilisations médicinales traditionnelles de *P. lentiscus*.

Mots clés: *Pistacia lentiscus*, phytochimie, toxicité, médecine traditionnelle, activités biologiques et pharmacologiques.

List of Abbreviations

µg:Microgram

ABTS:(2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid))

ATC: Aluminum Trichloride Calorimetric

ATP:Adenosine triphosphate

BSA: Bovine Serum Albumin

COX-2: Tolerability of selective cyclooxygenase 2 inhibitors

DM: dry matter

DNA: Deoxyribonucleic acid

DPPH :(2, 2-diphenyl-1-picrylhydrazyl)

E: equivalent

EC50: Half maximal effective concentration

ESI: equipped with an electrospray ionization

FC: Folin–Ciocâlteu method

FRAP: Ferric-reducing power

FRAP: Fluorescence Recovery after Photo bleaching

GA: Gallic acid

GC: Gas chromatography

HPLC: High-performance liquid chromatography

HPLC-DAD: high-performance liquid chromatography with diode array detection analysis

HPLC-DAD-MS: high-performance liquid chromatography

HPLC–diode array detection (DAD)–mass spectrometry (MS) analysis

HPLC-ESI-QTOF-MS: high-performance liquid chromatography with diode array coupled to electrospray ionization mass spectrometry

IC50: The median inhibitory concentration

IL1: Interleukin1

IL-1β: Interleukin 1 beta

LC-MS: Liquid Chromatography Mass Spectrometry

Mg: Milligram

MHA: Muller-Hinton agar

ML: Milliliter

Mm: Millimeter

MS: mass spectrometry

Q: quercetin

STD: standard

VEGF: Vascular endothelial growth factor

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Introduction

INTRODUCTION

Plants have provided man with all his needs in terms of shelter, clothing, food, flavors and fragrances as not the least, medicines. Medicinal plants are regarded as rich resources of traditional medicines and from these plants many of the modern medicines are produced.

The mastic tree (*Pistacia lentiscus*) has been evaluated by many scientific studies since it was used in folkloric medicine throughout the centuries in many regions and cultures. *Pistacia lentiscus* played a vital role in ethnomedicine as a plant with versatile applications for a variety of ailments, it is also noted for its nutritional value and minimal adverse effects (Azouzi et al.,2020).

The mastic tree is an evergreen shrub belonging to the Anacardiaceae family found widely in the Mediterranean region. *P. Lentiscus*, well known in Algeria by its common name in Algeria ‘‘darw’’, has long been used for respiratory ailments among other uses (Souilah et al.2023).

Studies have shown that *P. Lentiscus* has a rich composition of bioactive compounds such as its essential oil, fatty acids and polyphenols (Dahmoune et al., 2014; Garofulic et al., 2020). Studies have demonstrated that all the plant parts of *P. lentiscus* were abundant in phenolic acids and flavonoids (Rauf et al., 2017). Others studies confirmed the immensely positive effects of its phytochemical compounds, mainly its antioxidant activity and anti-inflammatory effect (Zitouni et al., 2016) along with other important medicinal and ethnobotanical uses such as an antimicrobial agent (Rauf et al.,2017), analgesic (Missoun et al.,2017) , wounds healing effect (Abidi et al., 2017).

It is in this context that this present work takes place, the main objective of which is provide an in-depth analysis of the different chemical compounds of *P. Lentiscus* as well its wide range of health benefits, pharmacological and ethnopharmacological aspects

This work consists of a bibliographical review, consists in particular of a botanical description of mastic tree, its bioactive phytochemicals and their effects and activities both in ethno pharmacological and medicinal applications, supported by studies of the therapeutic biological activities of *P. Lentiscus*.

Chapter I
Botanical study of
P. lentiscus

Chapter I: Botanical study of *P. lentiscus*

I.1 Anacardiaceae Family

I.1.1 Botanical description

The Anacardiaceae family includes trees, shrubs, and climbers with schizogenous resin canals (climbers exceptionally), pinnate or trifoliate compound leaves, usually alternating and lacking punctiform glands possessing panicle inflorescence (Bougherara, 2015). The plants of the Anacardiaceae family produce valuable resins and many of them are edible (Bougherara, 2015).

The composition of this family in terms of genera and species differs from author to author. According to Pell (2004), there are 82 genera and over 700 species. It includes about 600 species divided into 70 genera (Landau, S *et al.* 2014). The most recent classification of (Khoshkharam *et al.* 2022) counts more than 80 genera (table 01) and about 870 species.

I.1.2 Geographical distribution

This family primarily consists of plants that originated in tropic or subtropic regions. However, some species, notably pistachios, thrive in Mediterranean regions (Mertens *et al.*, 2016; Harrat *et al.*, 2018; Asma, 2019 and Mitchellet *al.*, 2022).

Table 1: Taxonomic hierarchy of Anacardiaceae Family.

	Scientific name
Kingdom	Plantae
Sub-Kingdom	Embryophyta (angiospermae)
Class	Dicotyledonae
Order	Sapindales
Family	Anacardiaceae

I.1.3 Plant's description

Different genera of Anacardiaceae have common characteristics are listed in the table 02.

Table 2: Common characteristics of the different genera of Anacardiaceae (Ghazali & Mohammad, 2014; Guo et al., 2023 and Manchester and Judd, 2022)

Organ	Description
Leaves	Deciduous or evergreen, but sometimes semi-evergreen. The leaves are composed of several leaflets. Foliage alternates, rarely opposite, without stipules. Leaflets mostly imparipinnate (but sometimes paripinnate). Some genera have simple leaves. However, this is rarer. Blade with entire margins (often-smooth margins). However sometimes may be crenate or toothed.
Flowers	The flowers are inconspicuous. Usually assembled in axillary or terminal panicles. Sometimes in racemes or spikes. The inflorescences have a very large number of flowers. In some cases several thousands. Actinomorphic flowers (symmetrical flowers). Calyx between 4 to 5 sepals. Often 5 free petals, but sometimes 4 in <i>Pistacia</i> (<i>pistachio</i>).w Number of stamens : 4 to 5 or 8 to 10
Fruits	Serval fruit forms in this family. Seeds with little or no albumen.

I.2 *Pistacia* genus

Pistacia is a genus of flowering plants belonging to the Anacardiaceae family, it contains some twenty (20) species, five (5) of which are popular, including *P. vera*, *P. Atlantic*, *P. terebinthus*, *P. khinjuk* and *P. lentiscus* (Landau, S et al., 2014)..

The *Pistacia* genus is characterized by its dioecious reproductive system (male and female plants) and by its homeochlamydic perianth of "naked" flowers. Based on morphological characters, the genus *Pistacia* is divided into four sections (Landau, et al., 2014).

Lentiscella (new world species), *Lentiscus evergreen*, *Butmela* (*P. atlantica* Desf.) and *Terebinthus*.

Different classifications have been proposed regarding the *Pistacia* genus. (Parfitt et al. Badenes 1997) suggested dividing the genus *Pistacia* into two sections: *Lentiscus* and *Terebinthus*, based on analysis of plastid restriction sites and morphological characters:

- *Lentiscus* section includes evergreen species with paripinnate leaves (no terminal foliage) and smaller seeds.
- However, hybridization is common between *Pistacia* species: in particular, what was once classified as *Pistacia aports* is now considered a hybrid of *P. lentiscus* (from section *lentiscus*) and *P. palaestina* (from section *terebinthus*).

In recent analysis of *Pistacia* phylogeny, based on internal ribosomal transcribed nuclear spacers (ITS) and nuclear DNA subsets, species from section *lentiscus* were not represented as a monophyletic group, but instead, as a few parallel clades with the section *terebinthus* clade nested there (Landau *et al.*, 2014).

I.3 *Pistacia lentiscus* species

P. lentiscus (figure 01) is a shrub in the family Anacardiaceae, also known as the mastic tree, and is part of the genus *Pistacia*. It thrives in a variety of soil types, including wastelands and shrub lands, in the Mediterranean basin (Isserin, 2007).



Figure 01: *Pistacia lentiscus* (Benselem, 2015).

I.3.1 *P. lentiscus* description

I.3.1.1 Taxonomy

The taxonomy of *P. lentiscus* according to Linnaeus (L., 1753) is given in table 03.

Table 3 : Taxonomy of *Pistacia lentiscus* According to Linnaeus (L., 1753) (Maameri, 2014).

Kingdom	Plantae (vegetal)
Sub -kingdom	Tracheobionta
Branch	Spermaphyte
Sub-branch	Angiosperm
Division	Magnoliophyta
Class	Magnoliopsida
Sub-class	Rosidae
Order	Sapindales
Family	Anacardiaceae
Type	<i>Pistacia</i>
Species	<i>Pistacia lentiscus</i>

I.3.1.2 Typical names

P. lentiscus has various vernacular names depending on the region, folkloric and dialectical names are listed in the table 04.

Table 4: Typical names of *Pistacia lentiscus* (Bougherara, 2015)

Regions	Dialectical names
England	chios mastic tree
Germany	Mastixbaum
France	Mastic tree, lentisque
Spain	Lentisco
North Africa	Derw, Darw (Arabic)
East Algerian	Gadhum
Berber	Tidekt, Tidekst
Arab Name	الضرو




I.3.1.3 Botanical description


The *P. lentiscus* shrub covers large areas in rocky and well-drained terrain, it is a slow growing plant. Its charcoal is of high value, and burns slowly (Claude, 2012).

I.3.1.3.1 Vegetative system

According to the studies of specialists and botanical research, we present a detailed description of the organs of *P. lentiscus* in the table 05.

Table 5: Characterization of vegetative apparatus of *Pistacia lentiscus*.

Organ	Description	Photo
Tree	Height of 3 -2 meters (Belakhdar,1997) Height varies from 4 to 5 meters (Lemaistre, 1995)	 <p>Shrub of <i>P. lentiscus</i>(Belfadel, 2009).</p>
The leaves	The leaves of this small woody plant consist of elliptical leaflets numbering 6 to 12 or 5 to 11, dark green above, light green below, with stepped petiole, rigid, veined, perennial erect in opposition, smooth skinned, beautiful, elliptique, light green, flowering in dense clusters Peduncle with narrow wings (Hans,2007).	 <p><i>P. lentiscus</i> leaves(Djedaia, 2017).</p>
Fruits	It is a spherical berry (2 to 3 mm), slightly cut in two, single-seeded, and filled with a stone of the same shape, initially red then becoming brown with its maturation which is completed in autumn. The color of the pulp passes from white to the final black while passing by the red. The brown fruits contain the majority of viable seeds, while the red and white fruits contain empty seeds.(Verdu, 1998 ; Garcia-Fayos, 2002)	 <p><i>P. lentiscus</i> fruits at different stages of ripening(Djedaia, 2017).</p>

Putty	When the stem of this plant is cut, a resinous juice called mastic flows out after distillation. It is obtained in summer, and this transparent resinous product gives off a strong balsamic smell, so it is used in the perfume industry (Belfadel, 2009).	
Lentisk oil	It is completely liquid at a temperature of 32 and 34 °C, its color is dark green (the berries can provide 20-25% of its weight), as it allows the precipitation of a white substance, subject to crystallization, which soon invades the whole oil and solidifies completely (Leprieur, 1860).	
Branch	Sinuuous and compressed branch, forming a narrow mass (Belfadel, 2009).	
Bark	When the bark is cut, a transparent resin flows from the plant with a strong odor, it is reddish on the young branches and becomes gray with time (Belfadel, 2009).	
Root system	The seed emits a very long root upon germination, sometimes reaching a depth of 7 meters, and a lateral root system that can reach a length of 5 to 10 meters from the tree top. These roots allow the pistachio tree to survive drought by seeking moisture in the soil and growing in arid regions (Boutboul, 1986; Lemaistre, 2000).	
Wood	The wood is white, yellow, pink and sometimes veined with yellow (Fatnassi, 2019).	

P. lentiscus resin (Abdeldjelil, 2016).

I.3.1.3.2 Reproductive system

Flowers (figure 02), of both sexes with a floral arrangement $5S+5E+3C$, are of brown color, forming dense clusters, which are at the origin of small red alleys, then turn to black at maturity (Boullard., 2001).

Male flowers: According to Jordano (1989), dark red male flowers have 8–10 stamens, produce 47,000–60,000 pollen grains per flower, and are arranged in inflorescences of 8–10 blooms. According to Ballouche (1986), pollen grains are subcircular or elliptic, with a main diameter of 25–30 μ m and a minor diameter of 22–27 μ m.

Female flowers: Yellowish green with cup with 3 or 4 lobes and ovary composed of 3 close carpels and 3 stigmas curved towards outside (Belfadel., 2009).



Figure 2 Female flowers (A) and male flower (B) of *P. lentiscus* (Benmehdi, 2012)

I.3.2 Geographical distribution

I.3.2.1 In the world

P. lentiscus is a small mound evergreen dioecious, preferring low-lying areas confined between sea level up to a height of 300 meters, in bioclimatic soils semi-dry, semi-wet and humid, warm, moderate and to some extent cool. The plant grows in different types of soils and resists to salinity. *P. Lentiscus* is considered to be one of the main components of mixed forests that represent the Mediterranean soil (Polese, 2010).

There are 11 species of the genus *Pistacia*. It has 4 vegetative geographical regions (figure 03): Mediterranean, Iranian-Turanic, Sino-Japanese and Mexican (Seigue, 1985).

It grows in the regions of the Mediterranean basin (from Morocco, the Iberian Peninsula and the Canary Islands in the west, through southern France and Turkey to Iraq and Iran in the east, via the Levant. It is widely cultivated on the Greek island of Chio (Belakhdar, 1997).

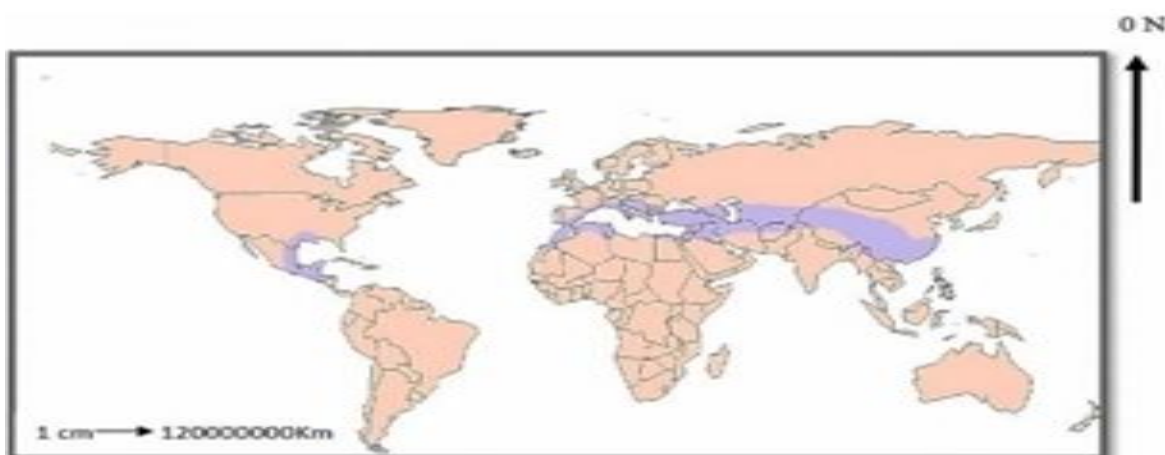


Figure 3 Geographical distribution of genus *Pistacia* (Belfadel, 2009).

I.3.2.2 In the Mediterranean

Around the Mediterranean Sea (figure 04), there are about 6 species of *Pistacia*. In the west, it is found in the Canary Islands, and in the north in Portugal, Spain, France, Italy, Greece and Turkey. In the south of the Mediterranean Sea, it is found in Morocco, Libya, Egypt, Algeria, Tunisia, Egypt, and in the eastern Mediterranean it is found in Palestine, Jordan and Syria. Pistachio lentils do not leave the Mediterranean and are very common in Corsica (Maire, 1926; Alyafi, 1979; Monjauze, 1965 and 1980; Hadj *et al.*, 1998).

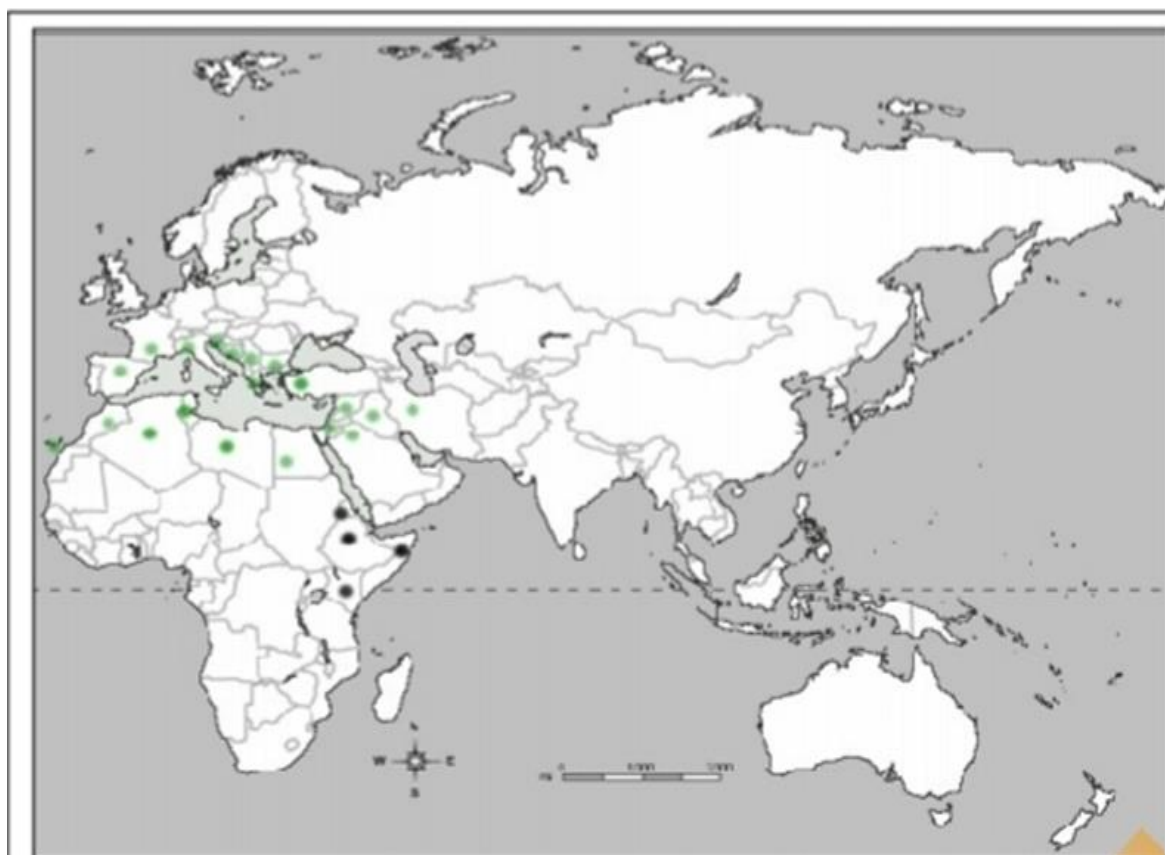


Figure 4: Distribution of *P. lentiscus* in the Mediterranean basin (AL-Saghir, 2006)

I.3.2.3 In Algeria

In Algeria, *P. lentiscus* (figure 05) is widely distributed in forests alone or in associations with other tree species like terebinth, olives, and carob, in all coastal areas up to 700 m above sea level, or in stony areas by the sea in Algeria (Dahmoune *et al.*, 2014). It grows in a variety of habitats along a climate gradient that varies in terms of solar radiation, temperature, and precipitation (Ait *et al.*, 2011).

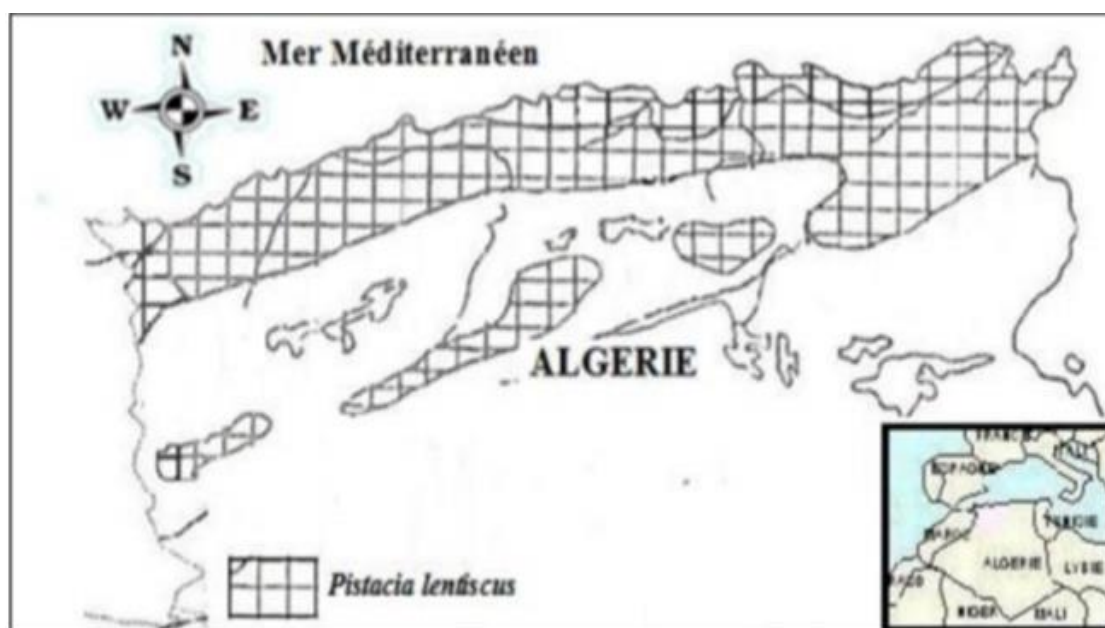


Figure 5: Distribution of *P. lentiscus* in Algeria (Quezel et Santa, 1962- 1993).

Chapter II

Phytochemical study

P. lentiscus

Chapter II : Phytochemical study of *P. lentiscus*

All therapeutic activities are linked to bioactive phytochemicals, in particular phenolics (Boudieb *et al.*, 2019). Various compounds belonging to different phytochemical groups have been identified in *P. lentiscus*, but its phytochemical composition varies according to the type of plant organ and the extraction method.

II.1 Phytochemical composition of the aerial part

It was found that the aerial parts are composed of essential oils, alkaloids, saponins, tannins and phenolic products (Elgubbi *et al.*, 2017). Mainly leaves and fruits are used for preparations of essential oils and also of water and alcoholic polyphenolic extracts. In Tables 06 and 07, the major compounds of the essential oils and quantitates phenolic classes extracts are listed. Hydro-distillation using Clevenger-type devices, and methanol solvent have been the more common methods to obtain, respectively, the oil and extracts from leaves and fruits. However, the oil obtained by hydro-distillation and the extracts by solvents can have different organoleptic profiles and chemical compositions.

Table 6: Chemical profiles of *P. lentiscus* essential oils aerial part

Plant Material	Test Assays	Main Components of Essential Oils	Origin	Reference
Aerial parts	GC, GC-MS	Longifolene (16.4%), Trans- β -terpineol (15.6%), terpinen-4-ol (7%), Γ -muurolene (5.7%), β -pinene (3.3%), α -pinene (2.8%)	Tizi-Ouzou (Algeria)	(Dob <i>et al.</i> 2006)
Aerial parts	GC, GC-MS	α -pinene (19%), Trans- β -terpineol (13.1%), sabinene (12.6%), β -pinene, (6.5%), (E)- β -ocimene (5.5%), longifolene (5.2%)	Oran (Algeria)	(Dob <i>et al.</i> 2006)
Aerial parts	GC, GC-MS	Longifolene (12.8%), γ -cadinene (6.2%), trans- β -terpineol (5%), α -acorneol (4.6%), γ -muurolene (4.2%), β -pinene (3.7%)	Algiers (Algeria)	(Dob <i>et al.</i> ,2006)
twigs	GC-FID, GC-MS	Terpinen-4-ol (25.2%), α -phellandrene (11.9%), β -phellandrene (10.2%),	Sardinia (Italy)	(Marengo <i>et al.</i> ,2018)

		γ -terpinene (10.1%), α -pinene (7.6%)		
Female flowers	GC-MS	α -limonene (28.7%), germacrene-D(23.7%), Elemol (6.7%), β -caryophyllene (6.6%), α -pinene (6.0%), bornyl acetate (3.7%)	Tunisia	(Yosr <i>et al.</i> ,2018)
Male flowers	GC-MS	β -caryophyllene(12.8%), germacrene-D(9.6%), elemol (8.9%), α -terpineol (7.8%), γ -cadinene (7.1%), bornyl acetate (6.2%)	Tunisia	(Yosr <i>et al.</i> ,2018)
Berries/methanol	HPLC-DAD-MS	Cyanidin3-O-glucoside(71%), delphinidin 3-O-glucoside, cyanidin 3- O arabinoside (28–31%)	Apulia (Italy)	(Longo <i>et al.</i> ,2007)

Table 7: Phenolic classes of lentisk's aerial part

Plant Part	Classes Detected	Type of Extract	Content	Analysis Method	Reference
Stems	Total phenols	Methanolic extract	121.4 mg GA Eq/g DM	FC	Amel, Z <i>et al.</i> ,2016)
Stems	Tannins	Methanolic extract	80.2 mg C Eq/g DM	Vanillin method	(Amel, Z <i>et al.</i> ,2016)
Stems	Total flavonoids	Methanolic extract	16.7 mg C Eq/g DM	ATC (Catechine: standard; Std)	(Amelet <i>et al.</i> ,2016)
Berries	Total flavonoids	Ethanollic extract Solid–liquid “soxhlet” extraction	13.4 mg Q Eq/g DM	ATC	(Belhachat <i>et al.</i> ,2017)
Twigs	Total phenols	Soxhlet extraction Solvents: [(hexane, ethyl acetate, methanol, ethanol) and water (infusion)]	48.7–302 mg GA Eq/g DM	FC	(Barbouchi <i>et al.</i> ,2020)

II.2 Fruits

P. lentiscus fruits contained a number of chemicals from several phytochemical categories.

II.2.1 Fruit's phenolic Compounds

The phytochemical test shows that the fruits of *P. lentiscus* have a very high content of anthocyanins, leucoanthocyanins, total tannins, gall tannins, flavonoids, glucosides and starch. On the other hand, we observe a moderate presence of mucilages and a total absence of saponosides, senosides, free quinones, coumarins, irridoids and alkaloids (Arab *et al.*, 2014).

Numerous studies have shown that *P. lentiscus* is rich in phenolic compounds (Bampouli *et al.*, 2014; Amel *et al.*, 2016; Barbouchi *et al.*, 2020). (Milia *et al.* 2021) has demonstrated total phenolic acids with concentrations of 538.0-4260.6 mg/kg from methanol/water fruit extract, along with total flavones 75.3-1222.9 mg/kg, total flavonols 24.2-377.4 mg/kg, total secoiridoids 12.6-366.8 mg/kg, and total phenols 12.6-366.8 mg/kg.

Fruits contained the following six phenolic compounds: gallic acid, catechin, 3,4-dihydroxyhydrocinnamic acid, benzoic acid, salicylic acid, and luteolin. (Geyikoglu *et al.*, 2016). Gallic acid, which is a characteristic of *Pistacia* species, is the building block of galloyl tannins. Fruits include digallic acid, 1, 2, 3, 4, 6-Pentagalloyl glucose, and gallic acid molecules, according to research by (Bhourri *et al.* 2010). Furthermore, fruits have been found to contain flavonoid molecules.

High quantities of total phenolic compounds (from 24.84 mg GAE/g dw (KO) to 46.07 mg GAE/g dw) and flavonoids (from 13.78 mg RE/g dw (RM) to 23.46 mg RE/g dw (TB) have been found by Trabelsil *et al.* (2016). The main polyphenols are phydroxybenzoic acid, gallic acid, cinnamylidene acetic acid, quinic acid, p-coumaric acid 4-0-glucoside, 5- galloylquinic acid, isomer of caffeoylquinic acid, 3,4,5 Otrigalloylquinic acid, quercetin, taxifolin, quercetin-3-Oglucuronide, luteolin 6,8-di-C-hexoside, oleoside and epirosmanol.

II.2.2 Fruit's terpenes and terpenoids

Studies have shown that the essential oil is one of the main components of the fruit (Alma *et al.*, 2004; Benamar *et al.*, 2010). The essential oil is made up of terpenoids and terpenes, mainly sesquiterpenes and terpenes. Limonene and pinene are the two main ingredients of the essential oil (Bouyahya *et al.*, 2019). The two monoterpenes are also responsible for the plant's flavor and aroma (Inbar *et al.*, 2004; Loi *et al.*, 2002; Melia *et al.*, 2021; Quartu *et al.*, 2012).

According to a phytochemical analysis of the fruit, sterols, triterpenes, oses, holosides, reducing sugars, mucilages, and alkaloids were all present in significant amounts (Barbouchi *et al.*, 2020).

According to (Fernando *et al.* 2000) and (Koutsoudaki *et al.* 2005), oxygenated monoterpenes and hydrocarbons are the main chemical components of essential oil. Unripe fruits contain more myrcene (54%) and α -pinene (22%), while ripe fruits contain less myrcene (19%), α -pinene (11%), and 3-carene (Boelens *et al.*, 1991).

Ripe oil fruits have phenolic component of seed oil as well, according to Mezni *et al.* (2015). Fruits have also been shown to contain α -pinene (13.35%), β -phellandrene (10.12%), α -phellandrene (10.45%), sabinene (7.01%), germacrene-D (6.86%), and β -caryophyllene (4.58%) (Ben Khedir *et al.*, 2016). According to Ammari *et al.* (2018), fruits include 4-oxobut-2-enoic acid (28.96%), α -myrcene (11.47%), 3-pentadecylphenol (8.51%), p-tolyl ester (8.36%), and amino formic acid (7.51%). Camphene (1.4%), α -terpineol (1.4%), α -pinene (12.6%), α -limonene (3.2%), and α -myrcene (75.6%).

II.2.3 The fixed oil of *P. lentiscus*

The fruit oil is extracted by turning the seeds into a fine powder or boiling dried fruit (in water), then it is powdered and crushed, and the water is separated from the oil (Ait youcef, 2006).

The lentil oil is dark green in color (it can provide 38% of the weight of the fruit), it is liquid at a temperature of 32 and 34°C, allowing the precipitation of a white substance, and is prone to crystallization (Leprieur, 1860).

The chemical composition of the fatty acids of the vegetable oil extracted from the berries of *P. lentiscus* is oleic acid, followed by palmitic acid and linoleic acid. Other acids are found in small proportions as the palmitoleic, stearic, linolenic, arachidic and gadolic acids. Four sterols are also found in the fixed oil: β -sitosterol (90%), campesterol, sterols and stigmasterol (Trabelsi *et al.*, 2012).

After conducting a recent study on 3 groups of fruits of *P. lentiscus*, it was found that there are 4 categories of glycerophospholipids (PL): phosphatidic acid (PA), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI). The predominant molecular species of glycerophospholipids consist of fatty acids C16:0 (palmitic acid), C18:1 (oleic acid), C18:2 (acidlinoleic acid) and minor species contain C18:0 (Stearic acid) and C18:3 (linolenic acid) (Trabelsi *et al.*, 2013).

II.3 Leaves

II.3.1 Phenolic compounds

Recent phytochemical analyses have shown that leaves of *P. lentiscus* are rich in bioactive phenolic components. The results of these analyses are shown in table 08. Leave's lentisk extracts

were found to be composed of total polyphenols, flavonoids, flavonols, tannins, anthocyanins, and proanthocyanidins. Depending on the type of extracts, one can observe a variation in the yield of these metabolites. Classically, phytochemical analyses were based on the use of specific colorimetric methods for each chemical family. Their contents were determined by spectrophotometry. According of the plant part, the total phenolic content in the leaves was significantly higher than that revealed in the stems and fruits in most of the previously described studies.

Table 8: Phenolic classes quantified in lentisk's leaves extracts

Type of Extract	Classes Detected	Content	Analysis Method	Reference
Ethanollic extract	Total phenols	0.90 Mg pyrocatechol Eq/g DM	Pyrocatechol is used as a standard in the FC(Folin-Ciocalteu method) and is equivalent.	Benhammou <i>et al.</i> ,2007
Aqueous extracts obtained from chloroform partition (solvent fractionation)	-Total Flavonoids -Tannins	- 44.25 mg Q Eq/g dry matter (DM) -997.8 mg TA Eq/g DM	- ATC (Aluminum Trichloride Calorimetric method: quercetin; Std) -BSA(Bovine Serum Albumin method)(Tannic acid: Std)	Atmani <i>et al.</i> ,2009
-Chloroform extract Methanollic extract -Aqueous extract -Ethyl acetate extract	- Total phenols - Total Flavonoids	-207 mg GA Eq/g DM -390 mg GA Eq/g DM -13 mg Q Eq/g DM -82.3 mg Q Eq/g DM	FC ATC	Saliha <i>et al.</i> ,2013
-Aqueous extract (decoction) -Ethanollic extract	Total Flavonoids	-3.1 mg Q Eq/g DM -8.2 mg Q Eq/g DM	ATC	Cheurfa <i>et al.</i> ,2015
Aqueous extract (infusion)	Total phenols	-119.7 mg GAE/g DM	FC	Ghenima <i>et al.</i> ,2015
Methanollic extract	Total Flavonoids	-19.1 mg C Eq/g DM	ATC (Catechine: standard; Std)	Amel <i>et al.</i> ,2016
Methanollic extract	Tannins	-121.5 mg C Eq/g DM	Vanillin method	Belhachat <i>et al.</i> ,2017
Methanollic extract	Total phenols	-216.2 mg GA Eq/g DM	FC	Bakli <i>et al.</i> ,2020
Ethanollic extract Solid-liquid "soxhlet" extraction	-Total phenols -Total flavonoids	-955.2 mg GA Eq/g DM -13.4 mg Q Eq/g DM	-FC -ATC	Belhachat <i>et al.</i> ,2017
Ethyl acetate fraction from ethanollic extract	Total flavonoids	-278.5 mg R Eq/g DM	ATC (Rutin: Std)	Bakli <i>et al.</i> ,2020
Soxhlet extraction Solvents: [(hexane,	Total phenols	-67.8-345.9 mg GA Eq/g DM	FC	Barbouchi <i>et al.</i> ,2020

ethyl acetate, methanol, ethanol) and water (infusion)]				
Methanolic extract (maceration)	Total flavonoids	-19,5 mg Q Eq/g DM	ATC	Amessis <i>et al.</i> ,2014

The separation, identification, and quantification of polyphenols were performed on several extracts of *P. lentiscus* leaves from Mediterranean countries. Several chromatographic techniques, including semi-preparative high-performance liquid chromatography (HPLC) and HPLC–photodiode array detection by comparison with authentic standards. High-performance liquid chromatography (HPLC)–photodiode array detection (DAD)–mass spectrometry (MS) (HPLC-MS) equipped with an electrospray ionization (ESI) was used. These techniques allowed us to obtain qualitative and quantitative information on the biochemical constitution of *P. lentiscus* leaves. Several metabolites including flavonoids, flavonols, flavanols, flavones, flavonoid glycosides, myricetin derivatives, anthocyanins, catechins, and different phenolic acids and their derivatives were identified (Table 09).

Several phenolic acids were detected, among which Gallic acid was recovered by several authors. These studies identified different metabolites including flavonoid glycosides, anthocyanins, and catechins and their derivatives. Among flavonoids, flavonol glycosides were found to be the most abundant class of flavonoids in the leaves. Myricetin derivatives was found to be the predominant flavonol glycoside. (Bozorgi *et al.*,2013) reported that quercetin-3-glucoside is the major flavonol in *P. lentiscus* as well as in other *Pistacia* species. Flavanols assigned as epicatechin, catechin, epigallocatechin gallate, and epicatechin gallate were recovered in several studies. Catechin was the most representative flavanol in *P. lentiscus* leaves.

Table 9: Phenolic compounds identified in lentisk's leaves extracts

Type of Extract	Compounds Detected	Analysis Method	Reference
Methanolic extract	Catechin β-glucogallin Quercitrin gallate	HPLC-ESI-QTOF-MS	Rodriguez <i>et al.</i> ,2013
Ethanollic extracts (maceration)	Gallic acid Catechin Syringic acid Ellagic acid Quercetin 3-O-rhamnoside Luteolin	Fourier transform infrared spectroscopy HPLC-DAD	Mehenni <i>et al.</i> ,2016
Ethanollic extract (maceration under stirrig)	Glucogallin, gallic acid, galloyl quinic acid digalloyl quinic acid, trigalloyl quinic acid	UHPLC-MS	Remila <i>et al.</i> ,2015
Ethanollic extracts	Hydroxybenzoic acid derivatives;	LC-ESI-MS/MS	Kirollos <i>et al.</i> ,2019

	Hydroxycinnamic acid derivatives; Hydroxy cyclohexane carboxylic acid derivatives		
Ethanollic extract	Gallic acid and galloyl derivatives of glucose Galloyl derivatives of quinic acid Myricetin Quercetin glycosides: delphinidin 3-O-glucoside and cyanidin 3-O-glucoside	Semi-preparative HPLC HPLC-MS analysis with 1H- and 13C NMR.	Romani <i>et al.</i> ,2002
Aqueous extract (Maceration under magnetic agitation)	1.5 or 3.5 Dicafeoylquinic acid Ellagic acid Catechin Luteolin-7-glucosid Isoquercetin Kaempferol rutinoid Rutin	HPLC-MS	Zahouani <i>et al.</i> ,2021
Aqueous extract (reflux heating)	Myricetin glucopyranoside Myricetin-3-O-rutinoside Quercetin-3,4-diglucoside Quercetin-3-O-rutinoside Quercetin-3-O-galattoside Myricetin-3-O-rhamnoside Myricetin-3-O-xylopyranoside Quercetin-3-O-glucoside	LC-MS	Foddai <i>et al.</i> ,2015
Methanolic fraction -from chlorformic extract by sonication	Shikimic acid, quinic acid, acid derivatives, gallic acid, Galbrol, proanthocyanidin prodelpinidin B-4, (dimer of gallocatechin and epigallocatechin), catechin or epicatechin, (epi)gallocatechin, (epi)catechin gallate, myricetin glycosides, myricetin derivatives, quercetin glycosides, quercetin O-galloylpentose, kaempferol, Luteolin	LC-ESI-MS/MS	Pacifico <i>et al.</i> 2014
Hydro-ethanolic extract (7:3 v/v)	Galloyl derivatives Catechin	HPLC	Azzaizeh <i>et al.</i> ,2013

II.3.2 Essential oil of lentisk's leaves

Mainly leaves and fruits are used for preparations of essential oil of *P. lentiscus*. Essential oil of lentisk's leaves is constituted by a mixture of terpenes and terpenoids, mainly monoterpenes and sesquiterpenes, which are also responsible for the characteristic smell and flavoring of the plant (Quartu *et al.*, 2012).

The chemistry shows that *P. lentiscus* essential oil is composed of up to 64 molecules constituted by a mixture of terpenes and terpenoids, mainly monoterpenes and

sesquiterpenes, which are also responsible for the characteristic smell and flavoring of the plant (Inbar *et al.*, 2004). The more recurrent components in *P. lentiscus* essential oil are represented by α -pinene, terpinene, caryophyllene, limonene and myrcene, with high variability in concentration depending on the Mediterranean country. It has been reported that terpenes *P. lentiscus* are more genetically than environmentally related (Franz *et al.*, 2010). Nevertheless, the environment of growing, seasonability of harvesting and kind of material (edible or not-edible parts of the plant) have to be considered when explaining the differences in chemistry of the oils (Barra *et al.*, 2007).

II.4 Resin

This substance is considered one of the resinous materials extracted from the trunks of the tree, and its quality varies depends on the type of trunk and the place of its cultivation. It consists of resinous lobes. When long incisions are made in the trunk of the tree and the large branches of the plant, its resinous sap flows out in the form of liquid that quickly freezes and remains attached to the tree in the form of fragile tears. Oval or long grains of yellow color, this mastic has a balsamic flavor of turpentine (Ait youcef, 2006).

Mastic is mainly made up of resin: ester of a triterpene alcohol and triterpene acids (masticodienic acid and oleanolic acid). It contains 2% volatile oil, 20% resinous substances, mucinic acid and bitter substances. This extract is used as an antiseptic, especially for the care of skin wounds (Ait youcef, 2006).

Mastic is also used in the treatment of stomach ulcers, oral health, colon and its disorders, and even cancer. It was also used in ancient Egypt to embalm corpses (Verlagsellschaft, 2007., Dietrich *et al.*, 2009., Lamendin, 2008). The resin is also effective against cough, diarrhea and bronchial diseases (Isserin, 2007).

Phytochemical analysis of mastic gum revealed that it contains a high percentage of an insoluble polymer (poly- β -myrcene), an acidic fraction containing acids and a neutral mastic fraction containing several neutral triterpene compounds with a phytosterol-type structure (Derong *et al.*, 2016). It contains a high percentage of monoterpene hydrocarbon, α -pinene and β -myrcene (Elgubbi *et al.*, 2017). In addition, the mastic water composition (a commercial aroma obtained during the steam distillation of mastic resin for the production of mastic oil) contains verbenone, terpineol, linalool and trans-pinocarveol (Arianna *et al.*, 2014). Several triterpenoid compounds have been isolated from neutral resin fractions such as tirucallool, dammaradienone, β -amyrin, lupeol, oleanolic aldehyde and 28-norolean-12-en-3-one (Bozorgi *et al.*, 2013).

Chapter III

Ethnopharmacological Uses of

P. lentiscus

Chapter III: Ethnopharmacological uses of *P. lentiscus*

III.1 Ethnopharmacological uses of *Pistacia* genus

Pistacia genus has a wide range of applications over the past centuries and present times. It is considered a plant of important medicinal value thus; it is used for the treatment of common diseases (table 10).

Table 10: Ethnopharmacological uses of *Pistacia* genus

Species	Ethnomedicinal uses	Used parts	Reference
<i>P. Lentiscus</i>	Abdominal aches, Eczema, Respiratory diseases, kidney stones	Bark and leaves	Souilah et al., (2022)
<i>P. Vera</i>	Abdominal aches, bruises and traumas, sores, chest aches	Fruits and Seeds	Rauf et al. (2017)
<i>P. Atlantica</i>	Abdominal aches, cough, anti-diarrheal, anti-diabetic	Fruits and leaves	Zitouni et al., (2016) Rauf et al., (2017)
<i>P. integerrima</i>	Liver pathologies, anti-inflammatory, gastrointestinal ailments, stomach aches, cough and fever, anti-diarrheal	Roots, gall and bark	Rauf et al., (2017)
<i>P. khinjuk</i>	Liver pathologies	Leaves	Porwal et al. (2022)
<i>P. Eurycarpa</i>	Skin Infections	Roots, leaves and bark	Rauf et al., (2017)

III.2 Ethnopharmacology uses of *P. lentiscus*

Pistacia species have been traditionally utilized for a variety of functions, the used plant parts include: resin, leaves, fruit, and aerial parts. Among the *Pistacia* genus *P. lentiscus* is the most extensively used plant of its genera in various regions of the world and has been in use for about 5000 years.

The Sardinians were one of the oldest civilizations who used the different parts of *P. lentiscus* as a medicine (Milia et al., 2021). Even the plant structure is different from a region to another but the utilization is generally very similar when it is used to treat the same disease (table 11). The oil is the most used compared to other parts of the plant (table 12).

Table 11: Ethnomedicinal uses of selected *Pistacia* species.

Regions	Utilized plant part	Ethnopharmacological reports and traditional usage	References
Sardinia, Italy	Leaf	Oral cavity inflammation and infection, tooth ache, osteoarthritis. Bronchitis, cough suppressant, antipyretic, allergies, asthma and ulcerations. Gastrointestinal disorders, wound healing and hemostatic.	Barra <i>et al.</i> , 2007 Ballero <i>et al.</i> , 2001 Loi <i>et al.</i> , 2002
Southern regions of Italy (Calabria and Campania)	Leaf	Mycosis, herpes, mouth inflammation and toothaches.	Leporatti & Ghedira(2009) Benítez <i>et al.</i> , 2012
Greece	Resin Aerial part	Intestinal disorders, hepatic inflammation, tooth disease, diabetes, diuretic and hypercholesterolemia. Stimulant, diuretic, hypertension, kidney stones, jaundice, cough, sore throat, eczema and stomach ache.	Benítez <i>et al.</i> , 2012 Hanlidou <i>et al.</i> , (2004) Benhammou <i>et al.</i> , (2008)
Spain	Leaf Fruit Tender bud	Dermatophytosis in cows Influenza and warts	Benítez <i>et al.</i> , (2010)
Turkey	Leaf	Eczema, diarrhea, throat infections, paralysis, kidney stones, jaundice, asthma, stomach discomfort, astringent, anti-inflammatory, antipyretic and antimicrobial.	Giner-Larza <i>et al.</i> , 2001
Iraq	Resin	Abdominal pain	Mati et de Boer (2011).
Jordan	Leaf Resin	Jaundice Heart burn and stomach pain	Janakat et Al-Merie (2002).
Libya	Resin	Immunostimulant and antimicrobial	Elgubbi <i>et al.</i> , 2017
Tunisia	Fruit	Edible usage, condiment, scabies, rheumatism, and antidiarrheal, Astringent, antipyretic, eczema, paralysis, throat infections, asthma, kidney stones, jaundice, antiatherogenic effect, antihepatotoxic effect, and gastrointestinal disorders, hypertension, cardiac diseases.	Trabelsi <i>et al.</i> , 2012 Leporatti et Ghedira (2009).
Morocco and North Africa	Leaf, Bark Leaf	Gastric analgesic Digestive disease, diabetes, hypertension, and heart disease	Fakchina et Elachouri (2014).
Algeria	Resin Leaf	Rheumatism, diarrhea, liver inflammation, tooth disease, diabetes, diuretics and hypercholesterolemia. Astringent and appetizing. Dyspepsia, peptic ulcer and stomach aches.	Saiah <i>et al.</i> , 2016

Table 12: Plant parts and its method of administration.

Plant part	Method of administration and causes:	References
Fixed oil extracted from ripe fruits	Topical application: Massage with oil for skin problems (eczema, brulures, bronchitis, asthma, sinusitis...) Internal uses: Drinking water extract for digestive and respiratory diseases. Mix with honey and drink (for lung congestion)	Beldi et al., 2021 Bammou et al., 2015 Miara et al., 2013 Djedaia(2017) Maameri-Habibatni (2014)
Woods or leaves	Internal uses: Infusion or decoction for digestive and respiratory troubles. Smoke obtained by burning or boiling the soft wood and leaves (osteoarthritis, bronchitis and allergies). External uses (Topical application): Disccated and ground to obtain a powder to which the oil or crema obtained is applied to the skin (skin diseases) or even use the whole parts of the plant. Administering extracts from the leaves as oral mouthwash, beverages or by directly chewing the soft stems and leaves	Miara et al., (2013,2018) Di Rosa (2018) Di Rosa (2018)
Fruits	Cooking.	Di Rosa (2018)

Chapter IV

Biological Activities of

P. lentiscus

Chapter IV : Biological activities of *P. lentiscus*

V.1 Antioxidant activity

Certain plants of the genus *Pistacia* demonstrated a varying potential for free radical elimination. The leaf extracts of *P.lentiscus* showed a prominent antioxidant effect (Benhammou *et al.*, 2008). The methanol extract of *P. lentiscus* was tested for antioxidant effect using DPPH and PRAP assays. The result showed a significant antioxidant activity (Gardeli *et al.*, 2008; Ourine *et al.*, 2010).

The polyphenolic extract of *P. lentiscus* fruit showed antioxidant and antimutagenic activities which are attributed to the gallic acid contained in the extract, which induced the expression of antioxidant and DNA repair genes (Abdelwahed *et al.*, 2007).

Pistacia genus plants demonstrated a strong anti-free radical potential that could medicate several diseases. The traditional use of *P. lentiscus* against jaundice led to research on its antioxidant properties. Because liver diseases cause significant oxidative stress, the aqueous extract of *P. lentiscus* tree was found to inhibit lipid peroxidation in rat liver homogenates (Yaniv *et al.*, Dudai, 2015).

Recent years have seen the publication of numerous works on the study of the antioxidant activity of several extracts from the different parts of *P. lentiscus*. The results of these studies are summarised in table 13.

Table 13: Antioxidant activity of *P. lentiscus*

Extract	Plant Part	Method	Significant Results	Reference
Ethanol extract	Leaves	ORAC test	Antioxidant capacity = 5865 $\mu\text{mol TE}/100 \text{ gE}$	Remila <i>et al.</i> ,2019
Aqueous extract	Leaves	DPPH assay	IC50 =9.86 $\mu\text{g}/\text{mL}$	Ghenima <i>et al</i> ..2015
Methanolic extracts	Leaves	DPPH assay	EC 50 = 0.121 mg/mL	Hemma <i>et al.</i> ,2018
Methanolic fraction from chlorformic extract	Leaves	DPPH assay ABTS assay	IC50 = 2.9 $\mu\text{g}/\text{mL}$ inhibition of 50% of ABTS•+(0.6 $\mu\text{g}/\text{mL}$ extract).	Pacifico <i>et al</i> ..2014
Phenolic extract from vegetable oil	Fruits	DPPH assay	IC50 = 37.38 mg/mL	Bouyahya <i>et al.</i> ,2017
Aqueous fraction obtained from	Leaves	Reducing power assay	IC50 = 50.03 lg/mL	Azib <i>et al.</i> ,2019

chloroformic extract		DPPH assay Activity against linoleic acid peroxidation	IC50 = 4.24 lg/mL IC50 = 0.82 lg/mL	
Methanolic extract	Leaves	DPPH assay β -carotene bleaching test	IC50 = 0.008 mg/mL IC50 = 0.12 mg/mL	Amessis <i>et al.</i> ,2014
Methanolic Extract	Aerial parts	FRAP	reducing power = 84.6–131.4 mmol Fe ²⁺ /L plant extract	Gardeli <i>et al.</i> ,2008
Ethanollic extract	Barries	DPPH assay ABTS assay Reducing power activity Assay	IC50 = 8.60 mg/mL IC50 = 8.65 mg/mL IC50 = 12.21 mg/L	Belhachat <i>et al.</i> ,2017

V.2 Antibacterial activity

P. lentiscus resin's antibacterial properties have been sufficiently demonstrated throughout several studies. Gastric inflammation is brought on by *Helicobacter pylori*. The *P. lentiscus* resin inhibited 50% of the pathogens at a concentration of 125 mg/ml and 90% at a concentration of 500 mg/m. Apoptosis and membrane protrusion were assumed to be the causes of the inhibitory mechanism (Marone *et al.*, 2001). In another study, the resin from *P. lentiscus* has been shown to have an impact on *Helicobacter pylori* in a randomized study. In some patients, a dose of 350 mg given three times daily for 14 days could completely eradicate the pathogen (Alma *et al.*, 2004).

Escherichia coli, *Staphylococcus aureus* and *Bacillus subtilis* showed variation in inhibition when exposed to the essential oil of *P. lentiscus* (Koutsoudaki *et al.*, 2005).

Magiatis *et al.*, 1999 show that the essential oil of *P. lentiscus* leaves has bacteriostatic activity, with zones of inhibition ranging from less than 7 mm for *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Candida tropicalis* and *Torulopsis glabrata* to 10 mm for *Staphylococcus aureus*, *Streptococcus epidermidis*, *Klebsiella pneumoniae*, *Escherichia coli* and *Candida albicans*. According to the literature, the antimicrobial activity of this essential oil

is probably due to the major compounds such as α -pinene (in Magiatis *et al.*, 1999). This has been verified by some authors (Magiatis *et al.*, 1999; Delazar *et al.*, 2004). It can also be attributed to phenols; constituents of essential oils (Katayama & Nagai 1960, Tassou et Nychas 1995). According to Tassou and Nychas (1995) and Shelef *et al.* (1980), Gram⁺ bacteria are more sensitive to *P. lentiscus* essential oils than Gram⁻ bacteria.

V.3 Healing activity

Boulebda *et al.* (2009) confirmed that topical application of the fatty oil from *P. lentiscus* fruits and its unsaponifiable fraction could have a therapeutic effect on wounds. *P. lentiscus* fruit oil has been shown to accelerate cutaneous wounds healing. Maameri-Habibatni (2014) observed that the healing rates of burns treated with *P. lentiscus* vegetable oils were much higher compared to the reference drug Cicatryl Bio. In the same way, Abdul Jalil (2016) showed that *P. lentiscus* fixed oil has a better therapeutic effect compared to the healing drug (sulfadiazine argentique). Moreover, the resin of *P. lentiscus* also reduces the duration of skin burn in rats (Haghdooost *et al.*, 2013).

The study published by Ben Khedir *et al.* (2017) demonstrated for the first time that the CO₂ laser fractional burn recovery benefits of *P. lentiscus* fruit oil. The findings showed that after eight days, the fruit oil-treated group had the highest percentage of wound healing contraction (100%) followed by the 'Cytol Basic' treated group (61.36%), and the untreated group (32.27%). In comparison to the other groups, the group that received fruit oil therapy showed reduced erythema, less crusting/scabbing, higher overall wound appearance scores, and a high collagen content (220.67 7.48 mg/g of tissue). Their ability to promote wound healing may be mostly due to their antioxidant, antibacterial and anti-inflammatory properties. Lentil oil is characterized by its capacity to stimulate and boost the immune system, and this stimulation will be the mechanism for wound healing (Oomah, 2001; Xu-guang Zhang, 2019).

V.4 Anti-inflammatory activity

Inflammation is one of the body's defenses carried on by the white blood cells in the body and the substances they produce, to treat an injury or to protect from infection by foreign organisms, including dirt, debris and fragments (Schorderet, 1992).

The polyphenols present in lentisk oil have anti-inflammatory properties, which are represented by the inhibition of enzymes involved in the inflammatory process (Skerget *et al.*, 2005). It inhibits the formation of pro-inflammatory cytokines (Mease, 2002). Remila *et al.*,

(2015) measured the release of IL-1 by macrophages exposed to adenosine triphosphate (ATP) or H₂O₂ to test the anti-inflammatory effect of leaves and fruit extracts. The investigation's findings showed that *P. lentiscus* leaves extract greatly decreased the amount of IL-1 that cells stimulated by ATP or H₂O₂ produced. As examined as separate fractions of the polyphenol combination, quercetin and gallic acid had a stronger inhibitory ability than fruits and leaf extract. These researchers claim that this is as a result of the leaves' higher overall phenol and flavonoid content as compared to the fruits, as well as the interaction of the pharmacological biomolecules in *P. lentiscus* extract.

In the study published by (Benkhedir *et al.*, 2016), the topical anti-inflammatory activity of *P. lentiscus* fruit oil was studied using a carrageenan-induced paw edema rat model. The diameter of the paw edema was measured for 5 hours at intervals of 1 hour to compare the topical anti-inflammatory activity to Inflocine. The rats were then scarified, and the inflamed paw tissue was excised in order to examine several histopathological and oxidative stress characteristics. Comparing *P. lentiscus* fruit oil to Inflocine, it had significantly more anti-inflammatory activity. After five hours, the percentages of edema inhibition were 70% and 51.5% ($p < 0.01$), respectively. *P. lentiscus* fruits oil and inflocine treatment resulted in significant increases ($p < 0.05$) in the activities of CAT, SOD, and GPX as well.

V.5 Hepatoprotective activity

Several studies have demonstrated the hepatoprotective activity of *P. lentiscus*. According to the study of Djerrou *et al.*, (2011) and Maameri (2014) the decrease in aspartate amino transaminase of rabbits treated with different doses of mastic tree oil could indicate an improvement in liver function due to a possible hepatoprotective activity of this oil.

Earlier, this activity was demonstrated by Al-Janakat and Al-Merie (2002) for the aqueous extract of pistachio lentisque (both boiled and unboiled) against Carbon tetrachloride hepatotoxicity. They concluded that pistachio lentisque is effective in the treatment of liver failure (jaundice) in rats.

V.6 Anticancer and anti-mutagenic activities

The genetic factor (DNA) is considered one of the causes that lead to cancer when it is damaged and among the reasons for its destruction, for example: chemical and carcinogenic substances, radiation, hormonal imbalances and genetic mutations (Mylène, 2004).

The essential oils extracted from *P. lentiscus* have antitumor activity because they contain phenolic components and flavonoids that have a preventive role in the development of cancer

(Kähköen *et al.*, 1999; Loutrari *et al.*, 2006; Moulos *et al.*, 2009). Also, it has been demonstrated that the essential oils obtained from *P. lentiscus* fruits and leaves have anticancer properties (Bouyahya *et al.*, 2019). Magkouta *et al.*, 2009 demonstrated that the use of intraperitoneal *P. lentiscus* essential oil (45 mg / kg body Weight) for the treatment of immunocompetent mice reduce significantly tumor volume without noticeable toxicity.

The crude extract of *P. lentiscus* fruits suppressed the development of melanoma cell lines. The B16F10 cells were strongly inhibited by the leaves and fruits (IC50 values of 56.40 and 58.04 g/mL, respectively) (Remila *et al.*, 2015). Douissa *et al.*, (2005) concluded that the essential oil extracted from the leaves of *P. lentiscus* harvested in Tunisia has an anti-mutagenic effect against aflatoxin (Hayder *et al.*, 2005).

V.7 Antiviral activity

Viruses are very sensitive to aromatic molecules in general and to extracts such as *P. lentiscus* extract. The latter contains monoterpenols known to have a significant effect on many diseases. Indeed, several serious viral diseases have been treated with *P. lentiscus* extract (Schuhmacher and reichling, 2003).

V.8 Antifungal activity

Fungi belong to the kingdom of organisms of the eukaryotic domain, with about 120,000 species (Semal *et al.*, 1993). Some fungi produce mycotoxins that can pose health risks to humans and animals (Giraud *et al.*, 2007).

The essential oil of *P. lentiscus* has a greater growth inhibiting activity of *Rhizoctonia solani*, *Fusarium sambucinum* and *Candida albicans* and *Fusarium* more important than *Penicillium* (El-Idrissi *et al.*, 2016).

V.9 Anti-ulcer activity

Stomach ulcers are open sores in the stomach lining that occur when the thick layer of mucus that protects the stomach from digestive juices erodes. Loss of appetite, nausea, weight loss are common symptoms of this ailment. Causes of stomach ulcers include: germ infection of the stomach caused by *Helicobacter pylori* (Pellequer, 1971). Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) causes stomach and intestinal ulcers due to increased acid secretion (Delchier, 1984).

The leaves and fruits of the pistachio tree are known to be rich in rutin, quercetin and naringenin. (Romani *et al.*, 2002; Luigia *et al.*, 2007). The role of quercetin is to produce mucus

and prevent the production of leukotrienes. Studies have shown that naringenin and quercetin play a role in protecting stomach cells and reducing stomach ulcers (Di Carlo, 1999). Other studies have shown that flavonoids inhibit PAF, which in turn leads to less gastrointestinal damage (Izzo, 1996).

V.10 Insecticidal activity

Essential oils have been used as insecticides for centuries and are among the safest and most effective alternatives to synthetic pesticides (Glitho, 2002). Insecticidal oils kill insects on contact by disrupting gas exchange in the respiratory tract and disrupting the function or structure of cell membranes. They also prevent the insect from feeding on oil-coated surfaces (Keane *et al.*, 1999). After conducting several tests to evaluate the ability of lentisk extract to exterminate insects, it was found to have a great ability to exterminate insects (Constant, 2009; Bouchekkif, 2017).

V.11 Anti-cholinesterase activity

Alzheimer's disease is a progressive brain disease that destroys brain cells and is characterized by changes in the brain that lead to deposits of certain proteins. Alzheimer's disease causes the brain to shrink and eventually die, and is the most common cause of dementia (Berchtold, 1998). Studies have shown that the concentration of acetylcholine, which is linked to the transmission of nerve messages, decreases in the brains of Alzheimer's patients, and this is due to the deterioration of the nerve cells that produce it (Karadsheh *et al.*, 1991). There are two types of cholinesterase: acetylcholinesterase (AChE) present in synapses and plasma, and type II: pseudocholinesterase (BChE) identified in the liver (Smiley, 1997).

An effective treatment for Alzheimer's disease is the use of anticholinesterase compounds (Marcoux *et al.*, 2002). *P. lentiscus* contains polyphenols, which are used in medicine to deactivate acetylcholinesterase (Atmani *et al.*, 2009; Amessis *et al.*, 2014). Flavonoids also slow the progression of Alzheimer's disease by inhibiting nerve cells atrophy (Williams *et al.*, 2012). The leaves of *P. lentiscus* contain flavonoids such as myricetin, quercetin and catechin, which in turn inhibit acetylcholinesterase (Benamar *et al.*, 2010; Falé *et al.*, 2013).

Chapter V

Toxicity of *P. lentiscus*

Chapter V: Toxicity of *P. lentiscus*

V.1 Toxicity of *Pistacia* genus

Few studies have been carried out on the toxicity of plants of the genus *Pistacia*. The methanolic extract of *P. integerrima* bark was found to be safe in a study on acute toxicity (Ismail *et al.*, 2012). Additionally, the *P. atlantica* fruits were found to be safe in investigations on acute toxicology measured over the course of two days. The cumulative non-lethal dose for *P. atlantica* fruit extract was 0.93 g/kg, while the LD50 was 1.66 g/kg (Nadri *et al.*, 2018).

Aqueous and ethanolic extract of *P. Vera* have been shown to be semi toxic in an acute toxicity study. Four groups of mice received ethanolic and aqueous extracts with the following doses administered (0.05, 0.2, 0.35, 0.5 g/Kg) for the methanolic extract and (0.04, 0.16, 0.28, 0.4 g/Kg) for the aqueous extract respectively, saline and morphine were used as negative and positive controls. The highest doses without fatality were 0.4 g/Kg for the aqueous extract and 0.5 g/Kg for the methanolic extract (Hosseinzadeh *et al.*, 2011).

V.2 Toxicity of the *P. lentiscus*

P. lentiscus soil consumption is generally considered safe, although the long-term safety has not been sufficiently investigated.

A study conducted by Djerrou *et al.* (2011), on the potential dermal irritant and subacute toxicity of the fixed oil of *P. lentiscus* fruit, was shown that *P. lentiscus* oil was minimally irritating to the eyes and skin after a single exposure, but could cause contact dermatitis and reversible skin thickening after prolonged use. Benalia *et al.* (2020) emphasized that the amount of alkyl salicylic acid in the oil should be determined by the manufacturers when using it in nutraceuticals or cosmetics, because the alkyl salicylic acids present in lentil fruit oil have skin irritating effects.

Another investigation on the Pistachio plant's toxicity was carried out by (Belkeloua *et al.*, 2012) on the fixed oil from the seeds of *P. lentiscus*. LD50 values obtained by single doses, orally and intraperitoneally administered in mice was 37 ± 1 ; [34.4–39.8] mg/kg body wt. po and 2.52 ± 0.2 ; [2.22–2.81] mg/kg body wt. ip respectively.

Djerrou *et al.*, (2013) assessed the safety of *P. lentiscus* fruit oil (PLFO) as a traditional topical remedy. To ascertain whether the PLFO could possibly cause irritation after just one application. Preliminary studies for skin and eye irritation were conducted on white N

ew Zealand Rabbits. Additionally; a subacute skin toxicity study was conducted in order to assess any potential unfavorable effects following the administration of PLFO for 28 days.

Based on the findings of the current study, the PLFO is classified as mildly irritating to rabbit's skin and eyes (Primary Irritation Index (PII) = 1,037; Ocular Irritation Index (OII) = 5,33 to 1 hour). PLFO has little irritating effects on the skin and eyes after a single exposure, although it may result in irritant contact dermatitis.

A study was conducted by Attoub *et al.*, (2014) where *P. lentiscus* oil (100µl) was administered orally in mice for 5 days. Body weight measurements did not reveal any weight decrease. When compared to control mice, the serum levels of LDH did not exhibit any appreciable statistical difference. When compared to the control group, blood, kidney, and liver function tests using *P. lentiscus* oil revealed no harm. Sections of the gastrointestinal tissues examined showed identical structural characteristics and no variations in cell growth. These findings point to a favorable safety profile for the short-term oral administration of *Pistacia lentiscus* oil as a single therapy for a range of gastrointestinal, respiratory, and skin conditions.

CONCLUSION

P. lentiscus is a valuable plant with a lot of ingenuity because of its potent and versatile pharmacological characteristics. Studies on this species revealed the value of *P. lentiscus* as a therapeutic herb. The information gathered and analyzed in this study shows that a good deal of research has been done on the chemical constituents, pharmacological effects, and biological functions of *P. lentiscus* fruits.

The goal of this study is to provide information on the botanical, ethnopharmacological, phytochemical, medical and toxicological aspects of *P. Lentiscus*.

Phytochemical analysis revealed an abundance of bioactive molecules including polyphenols, flavonoids, and tannins besides other molecules. *P. Lentiscus* contain essential oils, oils and phytochemicals such as fatty acids, steroids, terpenes and terpenoids, mainly monoterpenes and sesquiterpenes, which are also responsible for the characteristic smell and flavoring of the plant. Those compounds display antioxidant, anti-inflammatory, antimicrobial (antiviral and antibacterial), and protective liver and anticancer effects.

The ethnomedical applications of the mastic tree have been used to mitigate various disorders such as gastrointestinal, hepatic, urinary, pulmonary and skin. In fact, the medicinal value of *P. lentiscus* in popular medicine covers a wide range of diseases, mainly including inflammatory processes and infections.

Mastic tree has been a subject of some toxicological studies, findings mostly indicate its low toxicity which confirms that *P.lentiscus* is largely harmless and without many adverse effects

We made an effort to compile all the available pharmacological information including folkloric use and toxicity about *P. lentiscus*. We collected data about potential medical use of the plant and potential horizon for research. Taken together, all the above argumentations propose *P. lentiscus* as a nutraceutical, and also as a therapeutic agent against a wide range of diseases based on inflammation and infections.

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