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Biological and pharmacological study of *Pistacia
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Dedication

*To my father, to my family, whose support is so appreciated. I would
not be who I am today without you.*

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Abstract

The purpose of this study was to assess the lentisk seed oil from Hodna sub-arid region obtained by hot and cold extraction methods for the first time in terms of its physicochemical characteristics, phenolic contents and profile, tocols, and fatty acid compositions as well as its antimicrobial, antioxidant, wound-healing, and anti-inflammatory activities. Compared to the traditional procedure, which produced a yield of 5%, the cold pressing process produced a much higher yield of 15%. There are differences in the physicochemical properties of oils produced by hot extraction (HLHO) and cold pressing (HLCO). The oils are rich in unsaturated fatty acids, particularly linoleic and oleic acids. The phenolic content of the HLCO was higher than that of the HLHO. In HLCO, nine polyphenolic compounds were found, with quercetin and catechin being the most abundant, HLHO was found to contain seven compounds, with quercetin and sinapic acid being the most prevalent. α -tocopherol (59.96 mg/kg) and γ -tocopherol (19.64 mg/kg) were the main tocopherols in HLHO and HLCO, respectively. For HLHO and HLCO, the primary tocotrienols were β -tocotrienol (8.11 mg/kg) and γ -tocotrienol (8.02 mg/kg), respectively. Both mastic oils demonstrated the same ability to scavenge DPPH-radicals. There were only minor inhibitory effects on a panel of eleven microbial species. Both oils exhibited similar wound healing activity, which was comparable to the standard Cicatryl Bio®. The results of the anti-inflammatory activity of the phenolic compounds indicated that these compounds had significant inhibitory effects on COX-2. The method of extraction and the origin had an impact on the samples' physicochemical characteristics, phytochemical contents and antioxidant activity. In the food, cosmetics, and health industries, the investigated oils especially the cold-extracted one may serve as a natural source of potential bioactive components that may be substituted for manufactured ones or added to new products.

Keywords: Bioactive compounds, Biological activities, Hodna sub arid region, In silico study, *Pistacia lentiscus* oil.

Résumé

Le but de cette étude était d'évaluer l'huile de graines de lentisque de la région sub-aride de Hodna obtenue par des méthodes d'extraction à chaud et à froid pour la première fois en termes de ses caractéristiques physico-chimiques, teneur en phénol et profil, tocols, et ses compositions d'acides gras ainsi que ses activités antimicrobiennes, antioxydantes, cicatrisantes et anti-inflammatoires. Par rapport au procédé traditionnel, qui produisait un rendement de 5 %, le processus de pressage à froid a produit un rendement beaucoup plus élevé de 15 %. Il existe des différences dans les propriétés physico-chimiques des huiles produites par extraction à chaud (HLHO) et pressage à froid (HLCO). Les huiles sont riches en acides gras insaturés, notamment en acides linoléiques et oléiques. La teneur en phénol de HLCO était plus élevée que celle de HLHO. Neuf composés polyphénoliques ont été trouvés dans le HLCO, la quercétine et la catéchine étant les plus abondantes, le HLHO contenant sept composés, la quercétine et l'acide sinapique étant les plus répandus. - α -tocophérol (59.96 mg/kg) et γ -tocophérol (19.64 mg/kg) ont été les principaux tocophérols dans la HLHO et le HLCO, respectivement. Pour le HLHO et le HLCO, les tocotriénols primaires étaient respectivement le β -tocotriénol (8.11 mg/kg) et le γ -tocotriénol (8.02 mg/kg). Les deux huiles de mastic ont démontré la même capacité à éliminer les radicaux DPPH. Il n'y avait que des effets inhibiteurs mineurs sur un panel de onze espèces microbiennes. Les deux huiles présentaient une activité de cicatrisation similaire, comparable à celle du standard Cicatryl Bio®. Les résultats de l'activité anti-inflammatoire des composés phénoliques ont indiqué que ces composés avaient des effets inhibiteurs significatifs sur la COX-2. La méthode d'extraction et l'origine ont eu un impact sur les caractéristiques physico-chimiques, le contenu phytochimique et l'activité antioxydante des échantillons. Dans les industries de l'alimentation, des cosmétiques et de la santé, les huiles étudiées, en particulier celles extraites à froid, peuvent servir comme une source naturelle de composants bioactifs potentiels pouvant remplacer ceux fabriqués ou être ajoutés à de nouveaux produits.

Mots-clés: Activités biologiques, composés bioactifs, étude in silico, huile de *Pistacia lentiscus*, région sub-aride de Hodna.

الملخص

كان الغرض من هذه الدراسة هو تقييم زيت بذور الضرو من منطقة الحضنة شبه القاحلة التي تم الحصول عليها بواسطة طرق الاستخراج الساخنة والباردة لأول مرة من حيث الخصائص الفيزيائية الكيميائية، والمحتويات والصورة الفينولية، التوكولات، وتركيبات الأحماض الدهنية بالإضافة إلى مضادات الميكروبات، ومضادات الأكسدة، والتئام الجروح، والأنشطة المضادة للالتهابات. بالمقارنة مع الطريقة التقليدية، التي أنتجت عائدًا بنسبة 5٪، أنتجت عملية الضغط البارد عائدًا أعلى بكثير بنسبة 15٪. هناك اختلافات في الخصائص الفيزيائية الكيميائية للزيوت الناتجة عن الاستخراج الساخن (HLHO) والعصر البارد (HLHO). الزيوت غنية بالأحماض الدهنية غير المشبعة، وخاصة أحماض اللينوليك والأوليك. كان المحتوى الفينولي ل HLCO أعلى من محتوى HLHO. في HLCO، تم العثور على تسعة مركبات متعددة الفينولات، مع كون الكيرسيتين والكاتشين الأكثر وفرة. HLHO يحتوي على سبعة مركبات، مع كون الكيرسيتين وحمض السينايك هو الأكثر انتشارًا. α -tocopherol (59.96 ملغ/كغ) و γ -tocopherol (19.64 ملغ/كغ) هما التوكوفيرولات الرئيسية في HLHO و HLCO، على التوالي. وبالنسبة للتوكوتريلونات، في HLHO و HLCO كان التوكوترينول الأولي هو β -tocotrienol (8.11 ملغ/كغ) و γ -tocotrienol (8.02 ملغ/كغ)، على التوالي. أظهر كلا الزيوت المصطنعة نفس القدرة على القضاء على جذور DPPH. لم يكن هناك سوى تأثيرات مثبطة طفيفة على لوحة من أحد عشر نوعًا ميكريًا. أظهر كلا الزيوت نشاطًا متشابهًا في التئام الجروح، والذي كان مشابهًا لنشاط سيكاتريل الحيوي القياسي. أشارت نتائج النشاط المضاد للالتهابات للمركبات الفينولية إلى أن هذه المركبات لها تأثيرات مثبطة كبيرة على COX-2. كان لطريقة الاستخراج والأصل تأثير على الخصائص الفيزيائية الكيميائية للعينات والمحتويات الكيميائية النباتية والنشاط المضاد للأكسدة. في صناعات الأغذية ومستحضرات التجميل والصحة، قد تكون الزيوت التي تم فحصها وخاصة الزيوت المستخرجة باردة مصدرًا طبيعيًا للمكونات النشطة بيولوجيًا المحتملة التي يمكن استبدالها بالمكونات المصنعة أو إضافتها إلى المنتجات الجديدة.

الكلمات المفتاحية: المركبات النشطة بيولوجيًا، الأنشطة البيولوجية، منطقة الحضنة شبه القاحلة، دراسة حاسوبية، زيت بذور الضرو.

List of abbreviations

AOCS: American Oil Chemists' Society

ATCC: American Type Culture Collection

DPPH: 2,2-diphenyl-1-picrylhydrazil

GC/MS: Gas Chromatography coupled with Mass Spectrophotometry

GC-FID: Gas Chromatography-Flame Ionization Detection

HPLC: High Performance Liquid Chromatography

IGF-1: Insulin Like Growth Factor

IL: Interleukin

ISO: International Organization for Standardization

IUPAC: International Union of Pure and Applied Chemistry

LDL: Low Density Lipoprotein

MIC: Minimum Inhibitory Concentration

NF- κ B: Nuclear Factor

nm: nanomètre

NO: Nitric Oxid

NRRL: ARS culture collection

NSAIDs: Nonsteroidal anti-inflammatory drugs

OCDE: Organisation for Economic Cooperation and Development

PDB: Protein Data Base

TGF β : Transforming Growth Factor

TNF- α : Tumor Necrosis Factors

UV: Ultra Violet

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Introduction

Vegetable oils have been utilized by humans for decades and are still used today in fuel, food, medicine, and cosmetics. Seeds are a good source of edible oils because, in order to supply energy for germination and the initial phases of seedling growth, plants frequently store oil in their fruits and seeds.

Because of the growing need for oilseeds' nutritious vegetable oils, animal feeds, medicines, biofuels, and other oleochemical industrial applications, oilseeds have received greater attention lately (Guetarni et al., 2024).

Among its genera, *Pistacia lentiscus* is the one that is most widely utilized around the world; it is an oleaginous plant of the Anacardiaceae family, also known as the mastic tree (Trabelsi et al., 2012). Remarkably, like other Mediterranean areas, the semi-arid Hodna region, which is widely recognized for its significant usage of medicinal herbs, is a suitable habitat for the evergreen shrub *P. lentiscus* (Sarri et al., 2014). Many medicinal benefits of this plant are well recognized around the world (Aitmohand et al., 2021). The primary product made from this plant is the edible oil that is derived from the seeds (Ait Youcef, 2006).

Lentisk oil plays an important role as a medicinal product with high potential economic value. The fruit oil is valued for its beneficial properties serving as diuretic (Milia et al., 2021), an anti-inflammatory (Boutemine et al., 2018), an antiseptic (Mezni et al., 2015) and a healing agent for local skin diseases (Ben Khedir et al., 2016), burns, wounds (Boulebdia et al., 2009, Djerrou et al., 2010), gastric ulcers (Naouar et al., 2016, Boutemine et al., 2018), coughs and colds (Djerrou, 2014).

Many industries value the extraction of oil from oilseeds, and many techniques have been utilized in this regard depending on the potential uses of the derived oil. These days, mechanical methods of extracting oil are becoming more and more common as they require fewer steps and are safe and easy to use, and the produced oil can be processed swiftly (Ghiasi et al., 2022)

There are several techniques to obtain lentisk oil. The cold-press method, or cold extraction, is a mechanical extraction process that uses less energy and is ecologically benign. It is widely used to extract oil from a variety of seeds, although the traditional approach, or hot extraction, is the oldest and most widespread (Çakaloğlu et al., 2018).

This study represents the first investigation into *Pistacia lentiscus* oil derived from a sub-arid environment, specifically the Hodna region of Algeria. Its primary goal is to determine

how both this sub-arid origin and the extraction method (hot vs. cold) influence the oil's quality and functional properties, including its physicochemical parameters, fatty acid composition, phenolic and tocol profiles and content, as well as its antimicrobial and antioxidant activities. Furthermore, the research aims to assess the oil's therapeutic potential by evaluating its wound healing activity *in vivo* and its anti-inflammatory potential *in silico*.

Literature review

I. General plant information

Pistacia lentiscus belongs to the family of Anacardiaceae or Pistaciaceae, a diverse family with over 600 species split up into approximately 70 genera. Anacardiaceae are generally aromatic trees or shrubs, xerophytes and produce a rich variety of balms, resins and oleoresin (Bozorgi et al., 2013, Hemma, 2019). The genus *Pistacia* includes 11 species scattered in the northern hemisphere, including seven species that are spread from Central Asia to the Mediterranean basin (*P. lentiscus*, *P. palaestina*, *P. integerrima*, *P. atlantica*, *P. khinjuk*, *P. vera* and *P. terebinthus*), two species in East Asia (*P. weinmannifolia* and *P. chinensis*), where *Pistacia chinensis* is found in tropical Asia, reaching Myanmar and the Philippines, while two other species are found in the southwest of the United States and Central America (*P. texana* and *P. mexicana*) (Yi et al., 2008).

Some of these species have therapeutic properties recognized in traditional medicine in their countries of origin, as is the case for *Pistacia lentiscus* (Abdeldjelil, 2016). However, Algerian species belonging to the genus *Pistacia* are four: *Pistacia lentiscus*, *Pistacia vera*, *Pistacia terebinthus*, and *Pistacia atlantica*. These species are spontaneously dispersed in the Mediterranean basin (Quézel et al., 1962, Raho, 2017, Benalia et al., 2020).

I.1. Taxonomic classification

The classification of *Pistacia lentiscus* is summarized in Table 1.

Table 1: Classification of *Pistacia lentiscus* L.(von Linné, 1753)

Kingdom	Plantae
Branch	Spermaphytes
Sub branch	Angiospermes
Class	Dicotyledones
Order	Sapindales
Family	Anacardiaceae
Genus	<i>Pistacia</i>
Species	<i>Lentiscus</i>

I.2. Botanical description and vernacular nomenclature

Pistacia lentiscus, or mastic tree, is a shrub from 1 to 3 meters with a strong resinous odor. This species is characterized by tortuous and pressed branches that form a tight mass. Evergreen leaves are composed of 4 to 10 elliptical leaflets, leathery and shiny on top, glabrous, and the petiole is bordered by a green wing (Figure 1). The flowers are very

aromatic, unisexual in the form of a cluster, and form small racemes in the axils of the leaves. Male and female flowers grow on different shrubs; male flowers are dark red while female flowers are yellowish green. The flowering period is from April to June. The fruit is a globose berry (from 2 to 3 mm), monosperm, first red; in autumn it becomes black at maturity (Figure 2). The incision of the trunk drains a resinous juice called mastic (between 4 and 5 kg per tree); the distillation of this resin provides an essence used in perfumery (Belfadel and Boulebda, 2009, Ferradji, 2011, Beldi et al., 2021).

Pistacia lentiscus is known by various names:

In France: Pistachier lentisque, in Spain: Lentisco, in Italy: sondrio, in Arabic: Derw, in Eastern Algeria: Gadhoun (Boudieb, 2020, Beldi et al., 2021).



Figure 1: Morphological aspects of *Pistacia lentiscus*.



Figure 2: The fruits of *Pistacia lentiscus*.

I.3. Geographical distribution of *Pistacia lentiscus* L.

Pistacia lentiscus is a wild, thermophilic species, widely distributed in the extreme ecosystems of the Mediterranean region. It is found in Europe, Africa, and Asia to the Canary Islands. This species is adapted to the semi-arid climate of the Mediterranean and to the desert and saline soils (Rauf et al., 2017, Hemma, 2019). According to (Yi et al., 2008), the distribution of the 11 *Pistacia* species is shown in Figure 3.

In Algeria, *P. lentiscus* is found along the tell, in scrubland and especially the maquis, in forest areas and can develop on any type of soil, subhumid and semi-arid areas (Quezel and Santa, 1962, Zitouni, 2017). The tree is widespread in the forest alone or associated with other species such as turpentine, olives and carob (Dahmoune et al., 2014).

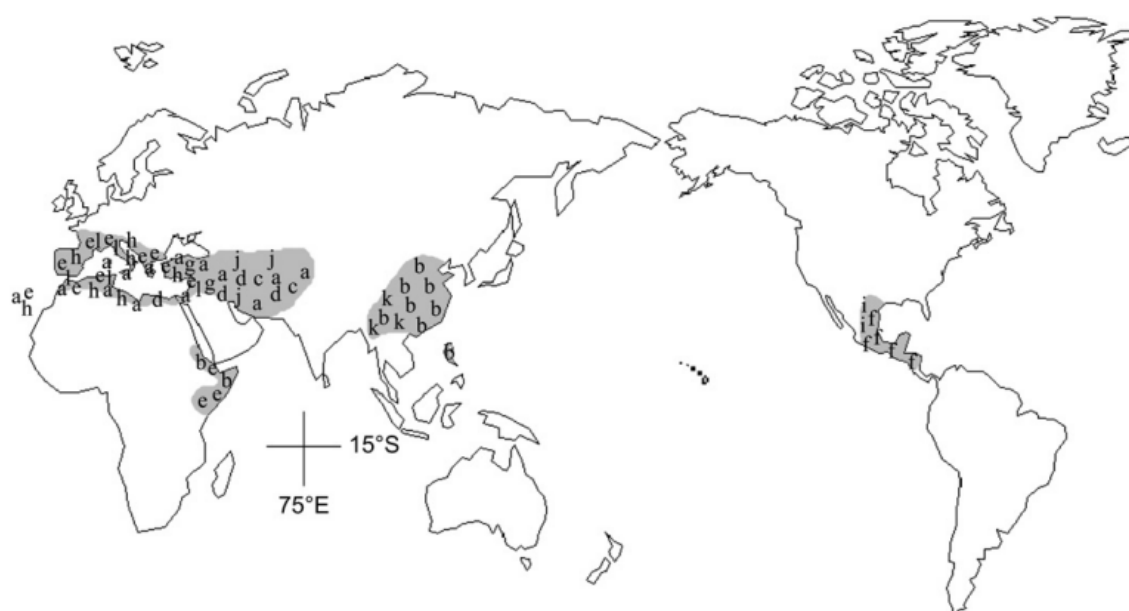


Figure 3: Distribution of 11 *Pistacia* species worldwide. a: *P. atlantica*, b: *P. chinensis*, c: *P. integerrima*, d: *P. khinjuk*, e: *P. lentiscus*, f: *P. mexicana*, g: *P. palaestina*, h: *P. terebinthus*, i: *P. texana*, j: *P. vera*, k: *P. weinmannifolia*, l: *P. saportae* (Yi et al., 2008) .

I.4. Use of *Pistacia lentiscus*

Pistacia lentiscus is known for its medicinal properties since ancient times (Boudieb, 2020); indeed, it was used by ancient Mediterranean civilizations such as the Egyptians and the Greeks (Djerrou et al., 2011). Its use is justified by its anti-inflammatory, antioxidant and antimicrobial potential (Belyagoubi-Benhammou et al., 2018). Different parts of this species (leaves, fruits, roots, and stems) were used (Zitouni, 2017).

The resin obtained from *Pistacia lentiscus* is used as an antiseptic of the respiratory system, antidiarrheal for children, to relieve abdominal pain, stomach pain, and peptic ulcer (Bammou et al., 2015, Arabi et al., 2017, Zitouni, 2017, Belyagoubi-Benhammou et al., 2018). This gum is considered an anticancer agent; it induces apoptosis and has anti-proliferative action against colon cancer cells, breast, liver, and stomach tumors (Bougherara Merzougui, 2015, Gacem et al., 2020). On the other hand, this gum has been used for a long time to prepare chewing gum in Iran (Zitouni, 2017) and for the manufacture of perfumes (Djedaia, 2017).

The aerial parts of the lentisk have been used to treat high blood pressure, coughs, stomach disorders, kidney stones, and jaundice (Djerrou et al., 2011). The leaves are applied topically to cure eczema, oral infections, diarrhea, hypocholesterolemia, asthma, and respiratory problems (Benabdelhak, 2015, Bougherara Merzougui, 2015, Cheurfa and Allem, 2015).

The most important product used of this shrub is its fixed oil (Abdeldjelil, 2016). In North Africa, from Algeria's eastern area to Tunisia, the fatty oil is traditionally used in the treatment of light burns, small injuries, erythema, and wound healing; it is also used orally against stomach ulcers and respiratory problems of allergic origin (Boukeloua and Belkhiri, 2009, Djerrou et al., 2011, Ben Khedir et al., 2016). Apart from its medicinal properties, anthocyanins of *P. lentiscus berries* are employed as food coloring in the food industry (Mazari et al., 2022).

I.5. Pharmacological activities

Several studies have shown the pharmacological power of different parts of *Pistacia lentiscus*. *Pistacia* fruit extract showed encouraging effects on diabetes in diabetic rats induced by streptozotocin, comparable to the reference medication glibenclamide (0.91 g/L)(Mehenni et al., 2016); an additional investigation verified that *P. lentiscus* raw gum reduced blood sugar (Rehman et al., 2015). Hamdi et al. (2023) investigated the antidiabetic and neuroprotective properties of *P. lentiscus* fatty oil and its unsaponifiable matter in vitro. The unsaponifiable matter showed strong antidiabetic action, while the oil showed strong anticholinesterase activity, concluding that these products might be used to treat type II diabetes and Alzheimer's disease.

The administration of *P. lentiscus* oil in combination with sodium arsenite decreased hepatic damage and disturbance of the pro- and antioxidant states (Klibet et al., 2016) and decreased ischemia-reperfusion injury to the liver in rats (Saidi et al., 2017). Also, it offers defense against intestinal irritation and colitis (Naouar et al., 2016).

After 8 days of treatment, the results of the first investigation on oil's effects on experimental inflammations in Wistar rats demonstrated the oil has strong healing properties against burns induced by the CO₂ laser (Khedir et al., 2017). This oil has anti-hyperlipidemic properties by reducing levels of LDL cholesterol and total triglycerides (Djerrou, 2014). Furthermore, *P. lentiscus* resin causes apoptosis in colon cancer cells of human HCT-116 (Balan et al., 2007).

The capacity of *P. lentiscus* oil produced with 2-MeOx to prevent nitrite formation generated by lipopolysaccharide (LPS) was used to evaluate its anti-inflammatory properties. The results showed that this oil suppressed nitrite production in a dose-dependent manner, with an increasing inhibitory impact with increasing oil content. The production of NO by the activated macrophages was suppressed by 75% at 50 µg/mL of oil and by 91% at a higher dose of 100 µg/mL (Chaabani et al., 2024).

The study of Ben Ameer et al. (2024) demonstrate that cold-pressed lentiscus oil strongly inhibited ADP-stimulated human platelet aggregation, α II β 3 integrin activation, and granule secretion. It also slightly inhibited aggregation induced by collagen and arachidonic acid.

Using the carrageenin-induced leg edema test and the HCl/ethanol-induced stomach lesions in rats, (Dellai et al., 2013) investigated in vivo the efficacy of aqueous and organic extracts of *P. lentiscus* leaves for their anti-inflammatory activity and antiulcerative properties. These extracts showed an anti-inflammatory effect and inhibition of gastric lesions in a concentration-related manner.

The results found by (Choi et al., 2022) showed that the supercritical mixture extract of the three plants *Pistacia lentiscus*, *Commiphora myrrha*, and *Momordica charantia* Linn. has a preventive and therapeutic action on inflammation and carcinoma of the oral mucosa.

The hydrolat of *P. lentiscus* was able to reduce the secretion of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α and the expression of the transcription factor NF- κ B as

well as CIC and ACLY, key players in metabolic reprogramming that occurs in inflammation (Santarsiero et al., 2020).

I.6. Chemical composition of the plant

Several extracts of *P. lentiscus* from the Mediterranean region were subjected to the separation, identification, and quantification of the various components. HPLC, HPLC-ESI-MS, HPLC-DAD-MS, and gas chromatography were among the chromatographic methods employed. These methods enable us to gather both qualitative and quantitative data on the biochemical composition of *P. lentiscus*. Numerous metabolites have been found, including polyphenols, flavonoids, and fatty acids (Table 2).

Table 2: Chemical composition of different parts of *P. lentiscus*.

Part of the plant and type of extract	Detected component	Analysis method	origin of the plant	reference
Methanolic extract from the leaves	Quercitrin gallate	HPLC-ESI-	Algeria	(Rodríguez-Pérez et al., 2013)
Ethanolic extract from the leaves	Catechin β -glucogallin	QTOF-MS		
Ethanolic extract from the leaves	Glucogallin, galloyl quinic acid, gallic acid, trigalloyl quinic acid, digalloyl quinic acid	UHPLC-MS	Algeria	(Mehenni et al., 2016)
Ethanolic extract from the leaves	Myricetin-3-O-glucoside, Myricetin-3-O-glucuronide, Myricetin-3-O-rhamnoside, Quercetin-3-O-rhamnoside, Catechine	HPLC UV/Vis PDA	Croatia	(Dragović et al., 2020)
Methanolic extract from the leaves	Quinic acid derivatives 3,4,5-O-trigalloyl quinic acid; 3,5-O-digalloyl quinic acid; Epicatechin-3-gallate; Luteolin-3-O-rutinoside; Quercetin-3-O-glucuronide; 5,7-	UHPLC-ESI-MS	Egypt	(El Bishbishy et al., 2020)

	dihydroxyflavone			
Methanolic extract from the leaves	Delphinidin 3-O-glucoside; Cyanidin 3-O-glucoside; Cyanidin 3-O-arabinoside	HPLC-DAD mass spectrometry (MS)	Italy	(Longo et al., 2007)
Hydromethanolic extract 80 v/v of vegetable fruit oil	Protocatechuic acid, Gallic acid, vanillic acid isomer, p-hydroxybenzoic acid, caffeic acid, p-coumaric acid, syringic acid isomer, ferulic acid, rutin, quercetin 3-O-glucoside	HPLC-DAD and UHPLC-ESI-MS/MS	Italy	(Siano et al., 2020)
Vegetable fruit oil	Tyrosol, Gallic acid, hydroxyphenylacetic acid, p-coumaric acid, Vanillic acid, salicylic acid, methoxycinnamic acid, carnosic acid, kaempferol, luteolin, naphtoresorcinol	HPLC-DAD/MSD	Tunisia	(Mezni et al., 2018)
Vegetable fruit oil	Palmitic, stearic, oleic, palmitoleic and linoleic acid	HPLC-DAD GC analysis.	Algeria	(Belyagoubi-Benhammou et al., 2018)
Essential oil of leaves and fruit	α and β pinene, Camphene, Myrcene, Sabinene and β -Phellandrene, p-Cymene, Germacrene, Limonene α and γ Terpineol, γ -Cadinene α -Caryophyllene	GC-MS	Algeria	(Bouyahya et al., 2018)

Vegetable fruit oil	stearoyloleoyl- linoleylglycerol (SOL), palmitoyl-dioleoylglycerol + (POO), palmitoyl- oleyllinoleoylglycerol (POL) Trioylelglycerol (OOO), α , β , γ and δ tocopherols Na, K, Ca, Mg, Fe et Cu	GC-FID	Algeria	(Dhifi et al., 2013)
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I.7. Antimicrobial activity

Different antimicrobial activities have been reported in previous studies; the results of these studies are shown in Table 3.

Table 3: Antimicrobial activity of different extracts of *P. lentiscus*.

Part of the plant and type of extract	Strains tested	Result	Reference
Vegetable fruit oil	<i>Eimeria acervulina</i>	It has a protective effect against the sequelae of coccidiosis in broiler chickens	(Rahmani et al., 2021)
Vegetable fruit oil	<i>Salmonella typhi</i> et <i>Klebsiella pneumoniae</i>	Similar activity to gentamicin	(Dhouibi et al., 2020)
Essential oil	<i>Helicobacter pylori</i> , <i>Escherichia coli</i> , <i>Morganella morganii</i> , <i>Enterobacter cancerogenus</i> , <i>staphylococcus aureus</i> and <i>enterococcus faecalis</i>	Good effect	(Arabi et al., 2017, Gacem et al., 2020)

The aqueous extract of leaves	<i>Escherichia coli</i> , <i>Enterococcus faecalis</i> , <i>Staphylococcus aureus</i> , <i>Bacillus cereus</i> , <i>Citrobacter freundii</i> and <i>Klebsiella pneumoniae</i>	Moderate effect	(Iratni, 2016)
Dichloromethanolic Extract, Ethanolic, Ethylacetate, Aqueous and Methanolic extract	<i>Listeria innocua</i> , <i>Micrococcus luteus</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i>	All leaf extracts were effective against the strains tested	(Salhi et al., 2019)
Methanolic and Aqueous Leaf Extract	<i>Staphylococcus haemolyticus</i> , <i>Staphylococcus aureus</i> , <i>Proteus mirabilis</i> and <i>Pseudomonas aeruginosa</i> ,	Good activity where methanolic extract has an inhibitory effect of 27 mm and 33 mm against <i>S. haemolyticus</i> and <i>S. aureus</i> respectively	(Alhadad et al., 2022)
Ethyl acetate fraction of ethanolic leaf extract	<i>Candida albicans</i>	Good activity with MIC= 0.1mg/mL	(Bakli et al., 2020)

I.8. Antioxidant activity

The antioxidant capacity of *P. lentiscus* is widely studied; various techniques were employed to assess it. The most used tests were: DPPH (2,2-diphenyl-1-picrylhydrazyl), that is, ferric reducing power (FRAP); the scavenging activity of free radicals; free hydroxyl radicals (HO); the carotene bleaching test; the oxygen radical absorption capacity test (ORAC); the phosphomolybdenum assay (TAC); hydrogen peroxide scavenging activity (H₂O₂); and the ABTS•+ test: 2.20 -azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (Sehaki et al., 2023). The antioxidant activity of different extracts of *P. lentiscus* is represented in Table 4.

Table 4: Antioxidant activity of different extracts of *P. lentiscus*.

Part of the plant and type of extract	Method	Result	Reference
Vegetable fruit oil	Scavenging activity of DPPH	Great reducing power (higher than ascorbic acid)	(Aouinti et al., 2014), (Bouyahya et al., 2018)
Vegetable fruit oil	Scavenging activity of DPPH	Varying between 8.11 and 94.00%.	(Benalia et al., 2020)
2-MeOx extract of oil	Scavenging activity of DPPH	Exhibited a high antioxidant potential to scavenge DPPH radical (IC ₅₀ =16.89 µg/mL).	(Chaabani et al., 2024)
Methanolic extracts (leaves and fruits)	Scavenging activity of DPPH, ferric reducing power (FRAP).	A strong reductive activity	(Hemma et al., 2018)
Essential oils of the fruit	DPPH, FRAP tests and ABTS.	IC ₅₀ = 29.64 µg/mL (DPPH), IC ₅₀ = 38.57 µg/mL (FRAP), IC ₅₀ = 73.80 µg/mL (ABTS)	(Bouyahya et al., 2018)
Ethanolic extract from the leaves	Scavenging activity of DPPH	The extract (3g/L) inhibited 95.69% of DPPH activity	(Benhammou et al., 2008)
Ethanolic extract from the leaves	ORAC test	Antioxydant activité = 5865 µmol TE/100 gE	(Remila et al., 2015)
Ethanolic fruit extract	DPPH ABTS	IC ₅₀ = 8.60 mg/mL IC ₅₀ = 8.65 mg/mL	(Belhachat et al., 2017)
Methanolic extract of leaves and	Scavenging activity of DPPH	EC 50 = 0.26 mg/mL for fruits and EC 50 = 0.121 mg/mL for leaves	(Hemma et al., 2018)

fruits		
Different extracts of leaves and fruit	Phosphomolybdenum (TAC) assay	Aqueous leaf extract has the highest TAC 488.16 mg AA/g extract. (Barbouchi et al., 2020)

I.9. Oil toxicity

While one research in mice found that oral oil administration at dosages ranging from 10 to 100 ml.kg⁻¹ caused mortality with an LD₅₀ of 37 ml/kg, another study in rabbits found that rectal usage of *P. lentiscus* oil had no detrimental effects on liver and kidney function. Moreover, *P. lentiscus* oil reduces CYP2E1 activity to target the hepatic activity of cytochrome P450, which calls for caution when used with other medications. The oil has a minor irritating impact on the skin (PII = 1.037) and eyes (OII = 5.33), according to research done on rabbits. Prolonged usage of the oil might result in irritating contact dermatitis (Gacem et al., 2020).

The cytotoxic impact of the *Pistacia* oil obtained with 2-MeOx was investigated. After treating RAW 264.7 murine macrophage cells for 24 hours at various doses, the RAW 264.7 macrophages' cell viability was not affected by extracts at 10, 50, or 100 µg/mL. The cell viability was 100% at 10 and 50µg/mL and very marginally reduced to 91.42% at 100 µg/mL. Based on these findings, the concentration range for oil was established at 10 to 100 µg/mL to evaluate its anti-inflammatory properties without compromising the survival of the cells (Chaabani et al., 2024).

II. Overview on skin physiology and healing

II.1. Skin structure

The skin is an integument that completely covers the body. It is a fundamental organ for the maintenance of an individual. It has a thickness of 0.5 to 5 mm, its surface is about 1.75 - 2 m², its weight reaches 3.5 - 4 kg. The skin is composed of three superimposed layers, from the surface to the depth, the epidermis, the dermis, and the hypodermis whose thickness is very variable (from 100µm to a few mm) and dependent on anatomical locations, subjects, sex, and age. Each skin layer consists of cells of different types that give them different functions. However, its integrity can be altered in different ways during life (burn, cut, tear,

etc.). A healing process is then put in place to fill the loss of tissue, allowing the skin to regain its barrier role (Tran, 2007, Laverdet et al., 2018).

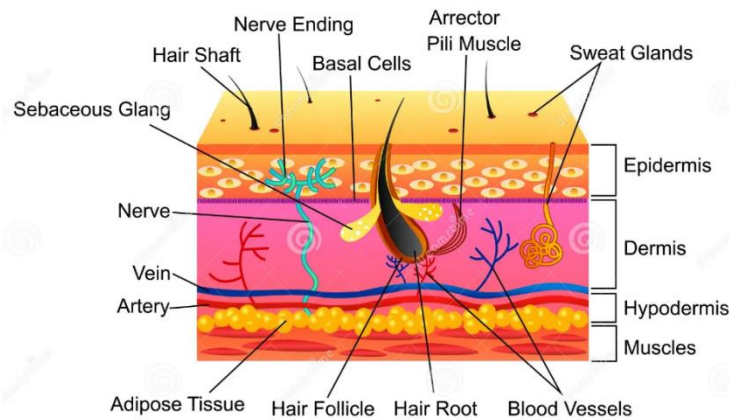


Figure 4: Skin structure (Dreamstime.com).

II.1.1. Epidermis

It is the most superficial layer of the skin. It is a squamous epithelium, stratified and keratinized, which contains neither blood vessels nor lymphatic vessels but contains many free nerve endings. It consists of four layers of cells, or keratinocytes, stacked on top of each other, which are from bottom to top: the basal layer, the spiny layer, the granular layer, and the stratum corneum. On average, the thickness of the epidermis is 0.1 mm. Despite the continuous renewal, its thickness is constant, thanks to the balance between the rapid multiplication of the deep basal cells and the permanent desquamation of the cells of the superficial stratum corneum (Tran, 2007, Maameri-Habibatni, 2014, Abdeldjelil, 2017).

The epidermis consists of a heterogeneous cell population, the majority of which are keratinocytes (at various stages of maturation), in addition to melanocytes, Langerhans cells, and Merkel cells, with the occasional presence of blood cells (Boukeloua and Belkhiri, 2009, Abdeldjelil, 2017).

II.1.1.1. Keratinocytes

These cells are the most abundant cells in the epidermis; these cells are differentiated by the process of keratinization by making keratin, a very resistant fibrous protein, which gives the epidermis its protective function. Keratinocytes are born at the basal layer, the deepest layer of the epidermis, and migrate vertically to the surface, differentiating to transform at the end of the course into corneocytes. The latter are dead, anucleated, and flattened cells, which

contain only keratin filaments; they are passively removed by desquamation (Hé, 2006, Ferraq, 2007).

II.1.1.2. Melanocytes

Melanogenesis is a process in which several enzymes catalyze the events that result in the production of melanin pigments in specialized organelles called melanosomes. Melanocytes have extensions between keratinocytes, through which they transfer their melanosomes. The melanocyte constitutes with the surrounding keratinocytes that it provides in melanosomes, the epidermal unit of melanization. Ethnic differences in skin color are determined by the size of the melanosomes and their mode of distribution. In wounds, the scar is usually discolored if the basal layer has been affected. However, melanocytes sometimes migrate late during cicatricial maturation, leading to skin recoloration, but often incompletely (Hé, 2006).

II.1.1.3. Langerhan cells

Langerhan cells are non-pigmented dendritic cells; they do not contain desmosomes or tonofibrilles; their cytoplasm contains specific granules, called Birbeck granules. Langerhans cells are immunocompetent cells from the bone marrow; they are a true immune sentinel of the epidermis; they play a role in non-specific immunity, presenting phagocytic antigen to T cells that react by inducing the immune response (Abdeldjelil, 2017).

II.1.1.4. Merkel cells

These are neuroendocrine cells located dispersed in the germinative layer, between the basal keratinocytes, and in contact with a free nerve termination. Merkel's cells are mechanoreceptors that also have inductive and trophic functions on the nerve endings of the epidermis and on the skin annexes via the many neuroactive substances they produce (Abdeldjelil, 2017).

- **Stratification of the epidermis**

The epidermis has 5 cell layers, from the inside to the outside:

- Basal layer (stratum germinativum): Cells in this layer gradually migrate to the surface by loading themselves into keratin while their nucleus disappears.
- Spine cell layers (stratum spinosum)
- Granular layer (stratum granulosum): cells no longer divide

- Clear layer (stratum lucideum)
- Stratum corneum (stratum corneum): this is the most superficial layer; the cells are keratinized and anucleated in the form of scales. The stratum corneum permanently peels due to a process that pushes cells from the epidermis to the surface while younger cells grow underneath. Once on the surface, flattened cells without a core are removed by washing, rubbing outer clothing, etc. (Tran, 2007, Boukeloua and Belkhiri, 2009, Maameri-Habibatni, 2014).

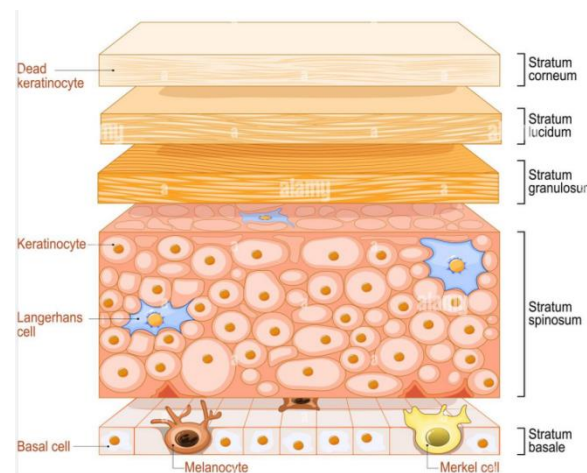


Figure 5: Structure of epidermis (Alamy.com).

II-1-2- Dermis

The dermis is the skin's supporting connective tissue; it has a complex structure thicker than the epidermis. It is composed of an extracellular matrix (fundamental substance), in which there are cells (fibroblasts, macrophages, and mast cells) and various fibers (collagens, elastics). It is a vascularized and innervated tissue that contains epidermal annexes (sweat glands, sebaceous glands, and hair follicles). The dermis is divided into two anatomical regions: the superficial papillary dermis, rich in cells, and the reticular dermis (in depth), rich in fibers. Depending on the anatomical location, the thickness of the dermis varies considerably; on average, it has a thickness of 2 mm but can reach 4 mm. The dermis is responsible for the texture, elasticity, strength, and healing of the skin (Hé, 2006, Ferrag, 2007, Tran, 2007).

The cells present in the dermis are grouped into two groups: the first group is represented by fibroblasts; the second group is composed of migratory cells. At the dermis are found the skin annexes such as hair bulbs, sebaceous glands, and sweat glands (Laverdet et al., 2018).

II.1.2.1. Fibroblasts

Cells of mesenchymal origin are the majority in the normal dermis. Fibroblasts produce several types of fiber (collagen, elastin, fibrillin); components of the extracellular matrix; enzymes (collagenases, matrix protease inhibitors); and different growth factors and cytokines (TGF β , IL-6, IGF-1, etc.) that are involved in tissue repair during healing (Hé, 2006).

II.1.2.2. Myofibroblasts

Myofibroblasts are intermediate cells between fibrocytes and smooth muscle cells, are rich in myofilaments, and are found in greater numbers in scars and some fibrous proliferations. Myofibroblasts have the ability to contract or relax, thus playing a role in the contraction of wounds during healing (Abdeldjelil, 2017).

II.1.2.3. Migratory cells

Migratory cells are of hematopoietic origin as macrophages, leukocytes, and mast cells. These cells are involved in the mechanisms of defense and immune response but also in healing thanks to the many substances they release (Abdeldjelil, 2017).

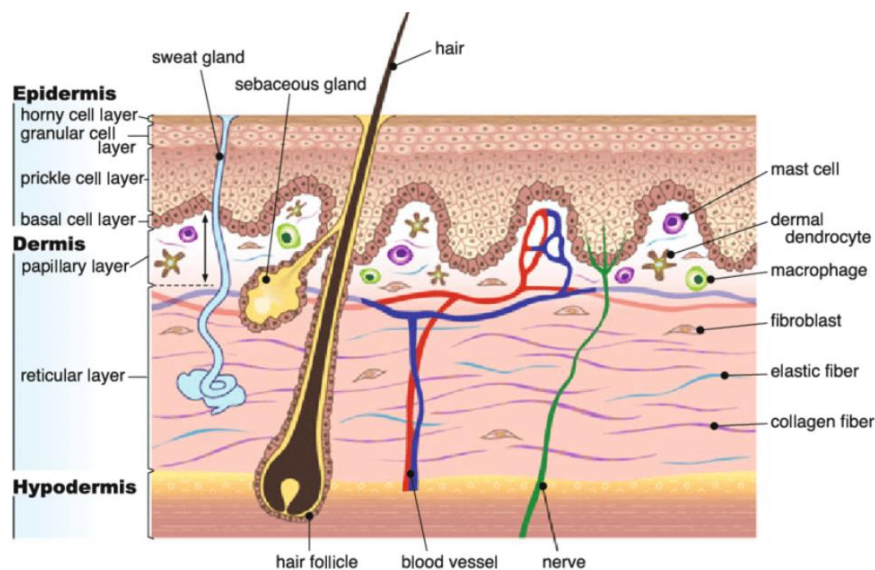


Figure 6: Structure of dermis (ibiologia.com).

II.1.3. Hypodermis

It is the deepest layer of the skin. It is a loosely richly vascularized connective tissue that connects the dermis to the deep conjunctive fascia, periosteum, or perichondrium. It consists of three components: fatty tissue formed by adipocytes grouped into lobules; interlobular septums, which are connective tracts that separate the fatty lobules; and vessels and nerves. The hypodermis contributes to the mobility and elasticity of the skin. In this layer are the sweat glands that make and expel sweat via small channels invisible to the naked eye (Hé, 2006, Tran, 2007).

II.1.4. Skin appendages

II.1.4.1. Nails

Nails are made of keratinized epithelial cells, protecting the ends of the hands and feet. Their growth is done from the nail matrix; because of the absence of desquamation, this process is uninterrupted but slow; it takes about 6 months to replace a nail of the hand, and from 1 year to 18 months for the regrowth of the nail of the big toe (Tran, 2007, Boukeloua and Belkhiri, 2009).

II.1.4.2. Bristles

They exist on almost the entire skin surface, depending on their location; some hairs have different names: hair, beard, mustache, eyelashes, and eyebrows. The hair is rich in keratin and consists of two parts: the root, implanted in a small cavity (follicle), located in the dermis, and a visible outer part, the stem. They have the role of protection against cold and mechanical pressure forces (Tran, 2007).

II.1.4.3. Sebaceous glands

They secrete sebum, a fatty substance consisting of fatty acids, tri-glycerides and cholesterol. It contributes to hydration and skin flexibility and also allows the lubrication of the hair, making it shiny. These glands are lodged near the hair follicles, forming the pilosebaceous apparatus (Tran, 2007).

II.1.4.4. Sweat glands

These are exocrine glands, simple tubules curled up that secrete sweat. There are two types of sweat glands that differ in function and in the composition of the sweat they excrete: eccrine sweat glands and apocrine sweat glands.

- **Eccrine glands**

Constantly secrete transparent, colorless, and odorless sweat, which has the main function of cooling the body by eliminating excess heat. Eccrine sweat is one of the constituents of the hydrolipidic film; it regulates pH, controls the development of saprophytic flora, and contributes to skin hydration.

- **Apocrine glands**

They secrete intermittently an abundant sweat, slightly yellow, more or less fragrant. These glands play a role in mutual recognition and delimitation of the territory (Tran, 2007, Maameri-Habibatni, 2014, Abdeldjelil, 2017).

II.2. Physiological functions of the skin

The skin is responsible for certain essential functions. It is at the same time an organ of protection against external aggressions, an organ receiver and producer of various substances, and finally a true organ of exchange and communication.

II.2.1. Protection function

- **Against mechanical damage**

The skin acts as a shock absorber and provides flexible and effective protection on three levels:

In the epidermis, the keratin of the stratum corneum constitutes a solid, continuous barrier; the hairs and coats reinforce this barrier.

In the dermis, elastic fibers and collagen fibers give the skin strength of tension and elasticity.

In the hypodermis, the fat cushion of the hypodermis protects the underlying muscles and bones from shocks and pressures (Ferraq, 2007, Tran, 2007).

- **Against chemical attack**

The stratum corneum and the film formed by sweat and sebum act as an impermeable barrier against the infiltration of certain substances from the environment into the internal

medium. However, this barrier is not totally impassable; some products can slowly penetrate through the skin to gain general circulation. This penetration can be used for the application of certain treatments. But it represents a danger when it comes to toxic products such as mercury (Ferraq, 2007, Tran, 2007).

- **Against dehydration**

The stratum corneum and the film formed by sweat and sebum prevent water loss through the skin, helping to protect the body from dehydration (Ferraq, 2007).

- **Against microorganisms**

The skin is the body's first defense against microorganisms. First, it is a mechanical protection provided by the stratum corneum and its keratinized dead cells, whose desquamation allows a reduction of microorganisms from the surface of the skin. The hydrolipid film, secreted by the sebaceous and sweat glands, improves this effect (Ferraq, 2007).

The second level is immune. Langerhans cells play a role of epidermis macrophages; they allow the presentation of the antigen to other immune cells (lymphocytes). Protection against microorganisms is also provided by the normal microbial flora that exists on the surface of the skin. This flora, called saprophyte, opposes the development of the so-called pathogenic flora that is generating diseases (staphylococcus aureus, streptococcus) (Ferraq, 2007, Tran, 2007).

- **Against UV**

The skin plays an important role in protecting against radiation, especially UV. These ionizing rays cause damage to the cellular DNA and the production of free radicals. The skin benefits from the double protection of the stratum corneum, which thickens, and melanin, whose secretion increases (Tran, 2007).

II.2.2. Thermoregulation function

The skin is an essential element in thermal regulation. It effectively contributes to maintaining the constant temperature of our body by involving: hair, subcutaneous adipose tissue, and sweat. Against the heat, the evacuation of excess heat is ensured by sweating and

active dilation of the small vessels of the dermis, where the blood cools by heat exchanges through the epidermis, allowing a heat loss. Against the cold, it uses the vasoconstriction of the small vessels of the skin, the insulating and thermogenic effect of the fatty tissue of the hypodermis; and the contraction of the small muscles of the hair «goose flesh» (Hé, 2006, Ferraq, 2007, Tran, 2007).

II.2.3. Sensory function

The skin is rich in sensory fibers and sensory receptors; it plays a role as a sensor of cognitive information. It contains receptors for different types of sensations: touch, pain, temperature (heat, cold), and pressure. The skin transmits these sensations to the brain, allowing the body to defend itself and adapt to the surrounding environment (Ferraq, 2007, Tran, 2007).

II.2.4. Metabolic function

The skin, through the adipose tissue of the hypodermis, constitutes an important reserve of energy that contains about half of all the fat stored in the human body. The skin also ensures the skin synthesis of vitamin D, thanks to the ultraviolet rays of the sun that induce the transformation of 7-dehydrocarbonesterol, or provitamin D3, into prevamine D3. The lack of skin synthesis of vitamin D can cause deficiencies (Ferraq, 2007).

II.3. Scarring of the skin

Healing is a biological phenomenon that allows an injured skin to recover its properties and functions. It is a dynamic process that takes place after an injury and involves soluble mediators (growth factors and cytokines), different cell types (endothelial cells, epithelials, blood, inflammatory, and immune cells), and interactions with the extracellular matrix.

The healing process is divided into three phases: the inflammatory phase (0 to 3 days), the proliferation phase and tissue formation (3 to 12 days), and finally the tissue remodeling phase (maturation). These phases are interdependent and overlap without strict separation in time. Most wounds or burns heal quickly within a few weeks when they are neither too extensive nor too deep. The healing time depends on intrinsic (wound depth) and extrinsic factors such as age, nutritional status, associated infection, bed rest, and comorbidities.

Healing is regulated and synchronized by a group of cytokines, such as PDGF, FGF, TNF, IGF, and TGF α and β . These are secreted by macrophages, lymphocytes, neutrophils,

thrombocytes, endothelial cells, and fibroblasts (Maameri-Habibatni, 2014, Abdeldjelil, 2017, Dahmani, 2019).

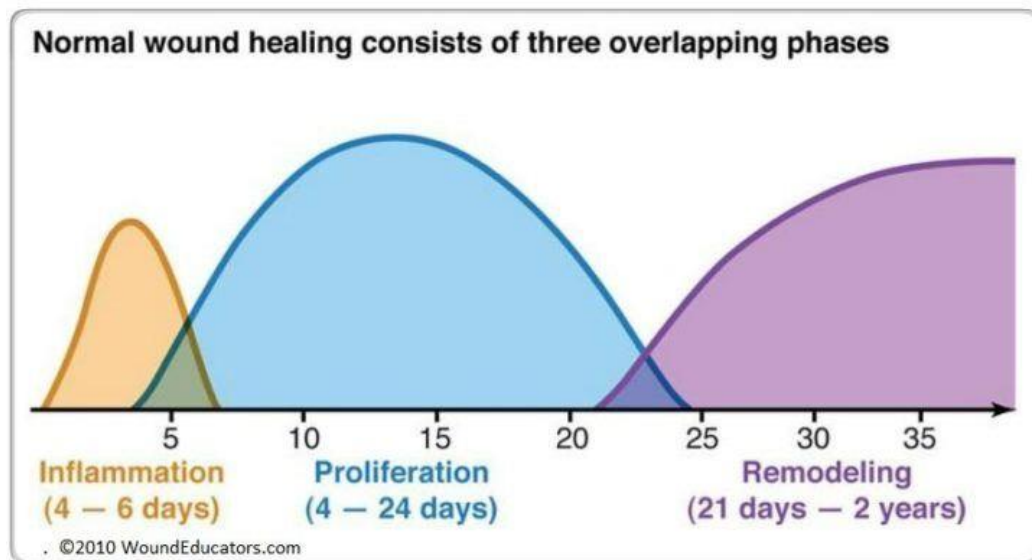


Figure 7: Chronology of the different phases of healing (woundeducators.com)

II.3.1. Description of the fundamental healing processes

II.3.1.1. Inflammatory phase

This phase includes the phases: vascular and detersion. It is quickly set up following a lesion; it begins a few minutes after the trauma and reaches its maximum between 3 and 5 days. It decreases rapidly until the 15th day, when it reaches a plateau, then decreases much more slowly. The goal of this phase is to bridge the induced tissue loss and stop hemorrhage through the vascular phase and the cell phase (Maameri-Habibatni, 2014, Abdeldjelil, 2017, Laverdet et al., 2018).

- **Vascular phase**

Blood loss from vascular breach is limited by local vasoconstriction with aggregation of blood platelets; the latter adhere to the endothelial walls, forming the hemostatic nail of Hayem, which ensures hemostasis I aire and initiates plasma coagulation. Activated platelets amplify hemostasis I air by inducing the adhesion of other platelets and strengthening vasoconstriction by the mediators they secrete. In addition, the damaged cells release thromboplastin that triggers a coagulation cascade that causes the transformation of fibrinogen into fibrin. The latter clumps with the platelets to form the blood clot called nail: hemostatic healing II air. This clot restores the tightness of the skin and serves as a matrix for cell

migration during the subsequent phases of healing. The activated platelets also release cytokines and various growth factors (PDGF, EGF, TGF β , IGF-1, etc.) from their granules, which play several roles during the healing process: recruitment and activation of leukocytes, fibroblasts, and macrophages; stimulation of mitosis of endothelial cells and fibroblasts; stimulation of collagen synthesis; angiogenesis; contraction and remodeling of the wound.

After the initial vasoconstriction, and on the effect of serotonin and histamine secreted by mast cells, a local capillary vasodilation takes over, which leads to an increase in vascular permeability and leakage of plasma and its macromolecular constituents (among them fibrinogen) out of the vascular area. This exudate, typical of acute inflammation, contains complement molecules, antibodies, enzymes, and several essential nutrients as a result of the healing process. In this phase, the recruitment and diapedesis of neutrophils and monocytes are observed; their penetration into the inflammatory site is due to vascular changes and controlled by a gradient of chemotactic mediators of various origins (Ferraq, 2007, Abdeldjelil, 2017).

- **Cell Deterision Phase**

It is a catabolic phase of phagocytosis and lysis that begins very early after the constitution of the wound and stops after elimination of any material that can hinder healing. Neutrophils are the first to reach the wound for infection control (phagocytosis of bacteria, tissue debris, and immune complexes). After a lifespan of less than 2 to 3 days during inflammation, these leukocytes die by releasing lytic enzymes from their lysosomes as well as metabolites with a phlogogenic effect (oxidizing radicals, LTB₄) that will participate in the lysis of necrotic cell debris. Neutrophils are quickly replaced by macrophages that are recruited from circulating monocytes and from «local» cells of the mononuclear phagocyte system. In addition to their predominant function of phagocytosis and collagenolysis, macrophages are also an important source of many mediators that play important roles during the healing process (cell recruitment and activation, matrix synthesis and angiogenesis). As soon as the deterision is finished, it leaves behind a clean focus containing several factors that will stimulate the actors of the following phases of healing (Abdeldjelil, 2017).

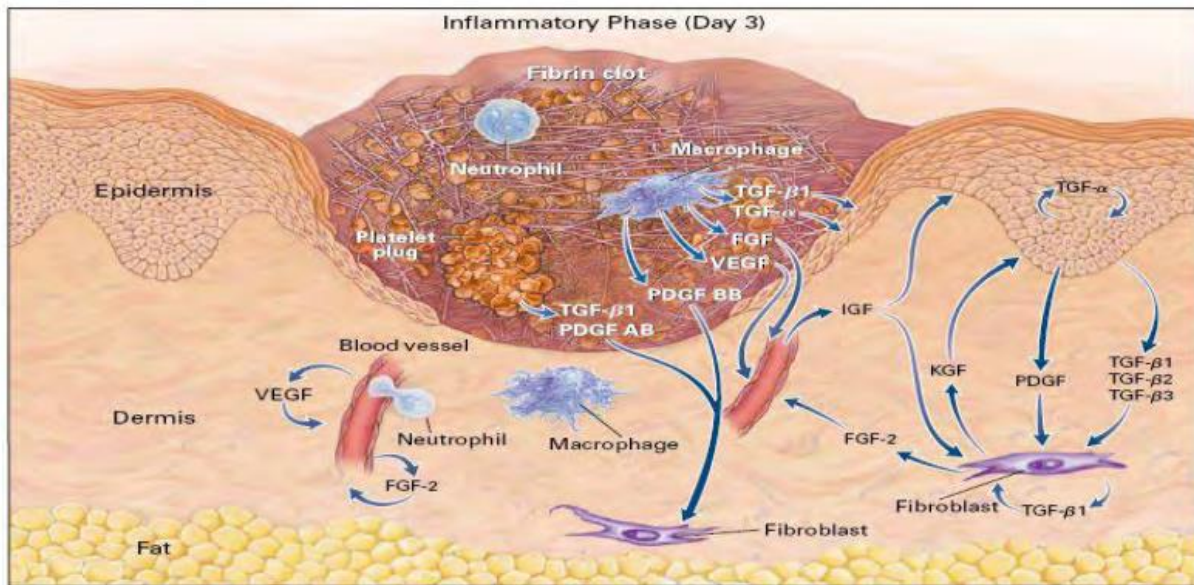


Figure 8: Illustration of the inflammatory phase (Maameri-Habibatni, 2014).

II.3.1.2. Proliferation phase (repair)

Begins after the inflammatory phase and aims to replace the provisional matrix with granulation tissue. This phase brings together two major anabolic phenomena: the formation of the granulation tissue and the epithelialization that will recover this tissue.

- **Formation of granulation tissue**

The granulation tissue is gradually set up to fill the loss of substance resulting from aggression and detersion. This transient tissue consists of fibroblasts (and myofibroblasts) that synthesize collagen and other elements of the extracellular matrix and a rich vascularization resulting from neo-angiogenesis. The formation of this tissue concerns only the areas of the wound properly prepared during the detersion phase.

Within 24 to 48 hours of the wound formation, the migration of fibroblasts begins. Their recruitment depends on the chemotaxis exerted by mediators from platelets, macrophages, and certain lymphocytes. The ability of cells to migrate and colonize the extracellular matrix depends on the proteolytic activity of various proteinases, most of which are secreted by fibroblasts. Once migrated to the wound, the fibroblasts multiply and begin their synthesis activity to fill the loss of substance.

Angiogenesis is the process of growing new blood vessels (neovascularization) from pre-existing vessels. Angiogenesis and fibrogenesis are interdependent phenomena that progress simultaneously. The formation of neocapillaries allows the supply of blood and nutrients

essential for fibrogenesis. The key element in the induction of angiogenesis is the macrophage, thanks to the many mediators it produces. Neovascularization requires stimulation, migration, and proliferation of endothelial cells of vessels adjacent to the wound. The activation of the endothelial cells of the postcapillary veins is under the effect of serotonin and histamine secreted by mast cells; these activated cells secrete various substances such as the enzymes "plasminogen activator", plasmin; collagenase, etc that are capable of disintegrating basal membranes and surrounding structures. The migration and proliferation of endothelial cells requires additional stimulation by chemotactic factors and growth factors produced by several cells (macrophage keratinocytes and fibroblasts). Among these factors, VEGF (vascular endothelial growth factor) is the most powerful angiogenic factor. The proliferation of endothelial cells allows the formation of tubular structures that unite with each other and gradually differentiate into arterioles or veins.

Fibroblasts begin by synthesizing proteoglycans, polysaccharides, and different glycoproteins, including fibronectin, to form the new fundamental substance. They also synthesize collagen under the influence of various mediators released mainly by macrophages and endothelial cells (FGF, TGF β , EGF, PDGF). When fibrin is degraded, collagen is deposited to replace it (Hé, 2006, Maameri-Habibatni, 2014, Abdeldjelil, 2017, Laverdet et al., 2018).

- **Contraction of the wound**

It allows the decrease of its surface thanks to a centripetal movement of the edges of the wound. This contraction is inconsistent and depends on the nature of the wound, its location, its healing mode, the importance of loss of substances, and the constitution of the skin. Contraction begins when the granulation tissue completely fills the loss of substance and stops when the margins of the wound come into contact (Abdeldjelil, 2017).

- **Epithelialization**

Epithelialization is a necessary step to restore the continuity of the skin. Epithelialization begins in the first 24 hours, especially in superficial wounds; it is fully completed after 2 weeks. Its duration, years of deep wounds, depends on the quality of the granulation bud. Basal keratinocytes of the wound banks (but also hair follicles and channels of eccrine glands) undergo a series of morphological changes and project lamellipodis. They are released from their dermal attachments and subsequently begin a migration to the deficit areas centripetally,

and sometimes centrifugally in case of the presence of intact epidermal islands. When the cells come into contact with the epithelial cells of the opposite edge, the epithelial migration ends. Cell migration alone is not sufficient for epithelial repair when the loss of substance is extensive; then it requires an intensification of the mitosis of the epithelial cells, which concerns essentially the peripheral epithelial cells far from the margins of the wound. In the presence of a crust or clot, epithelial cells migrate under the crust and secrete various proteases and collagenases that are capable of dissolving the base of the crust that falls once the epithelial cells have covered all the loss of substance (Hé, 2006, Abdeldjelil, 2017).

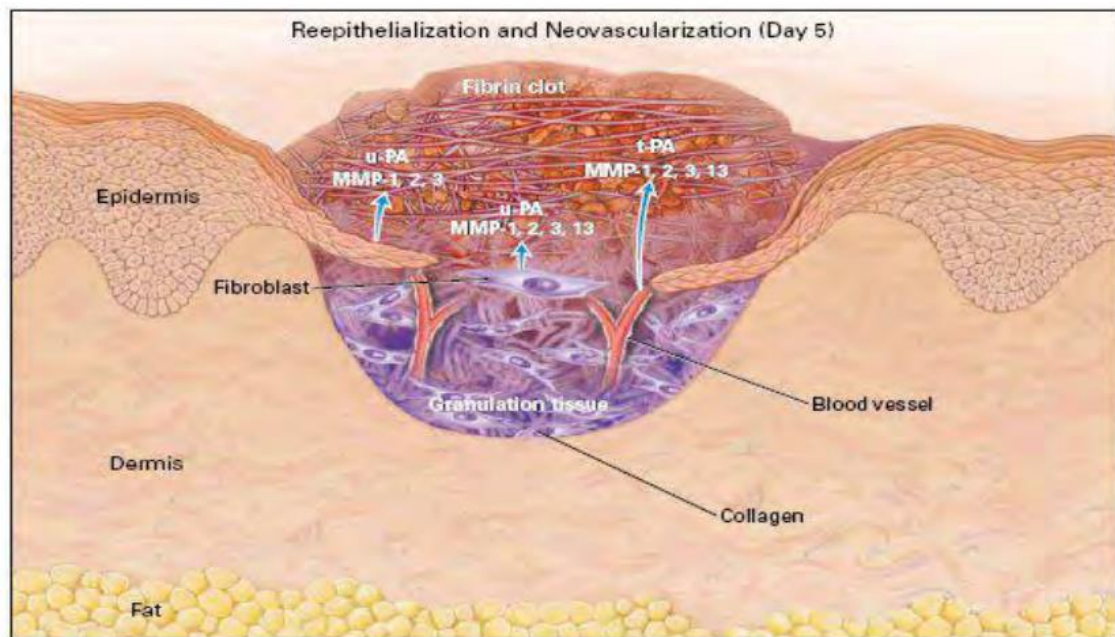


Figure 9: Illustration of proliferation phase (Maameri-Habibatni, 2014).

II.3.1.3. Tissue remodeling phase (maturation)

This is the last and longest step in the healing process. It begins after closing the wound, with regression of granular tissue that can persist for 2 years. The contraction of the wounds is completed around the 21st day associated with maximum collagen content. Initially necessary for cell migration and proliferation, fibronectin and hyaluronic acid are gradually lysed and replaced by elastic fibers, collagen, and glycoaminoglycans, constituting a matrix more resistant to tensile forces. Various elements are involved in this phenomenon: cells, such as polynuclear and macrophages, and enzymes, such as proteases synthesized by fibroblasts. These elements intervene in the remodeling phenomena by promoting the lysis and synthesis of new molecules that are better oriented and organized (Maameri-Habibatni, 2014, Laverdet et al., 2018).

Experimental part

Materials and Methods

I. Materials and Methods

This study concerns the evaluation of the fixed oils of *Pistacia lentiscus* L. The oils were extracted from the fruits by two methods, namely the traditional method (hot extraction) and the cold pressing method. The first step, carried out *in vitro*, is intended for the phytochemical and physicochemical study of oils and the evaluation of their antioxidant and antimicrobial effects. This part was carried out at ENS Kouba, in the quality control and compliance laboratory «Bedrane Younes Laboratory», and in the oil laboratory at Manisa Celal Bayar University in Turkey. The second part *in vivo* consists in evaluating the wound healing activity of our oils. This part is developed at the level of the pet shop of the Faculty of Science of M'hamed Bougara University in Boumerdes; the third part consists of performing the molecular docking of the main bioactive compound.

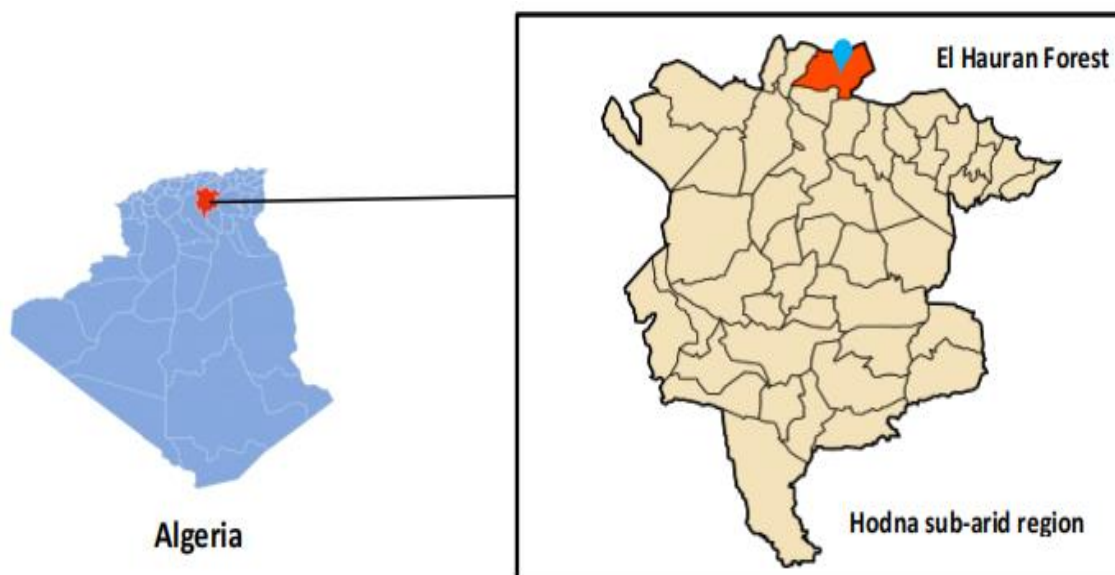


Figure 10: Harvesting site of *P. lentiscus* fruits.

I.1. Plant material

The fruits were harvested in the region «El Hauran Forest» in Msila (a sub-arid region in the North East of Algeria) in December 2021. Fruits with a semiblack or black pigmentation stage were chosen, avoiding the green color. Subsequently, the branches and leaves harvested with the fruits were cleared, and the quantity was divided into two parts, one part for traditional extraction and the other for cold extraction.

I.2. Method of oil extraction

I.2.1. Cold extraction

The fruits were cleaned and air-dried at ambient temperature for 10 days. Then the oil was extracted by cold pressure. In this process, we used a COMAF-type endless screw oil press with a capacity of 5 kg/h, which allows the obtaining of blackish oily liquids that are collected in a container. A dry cake was obtained as waste. Finally, the oily extracts were filtered using filter paper, and the oil was collected (Figure 11).



Figure 11: Operation of extraction by cold pressing.

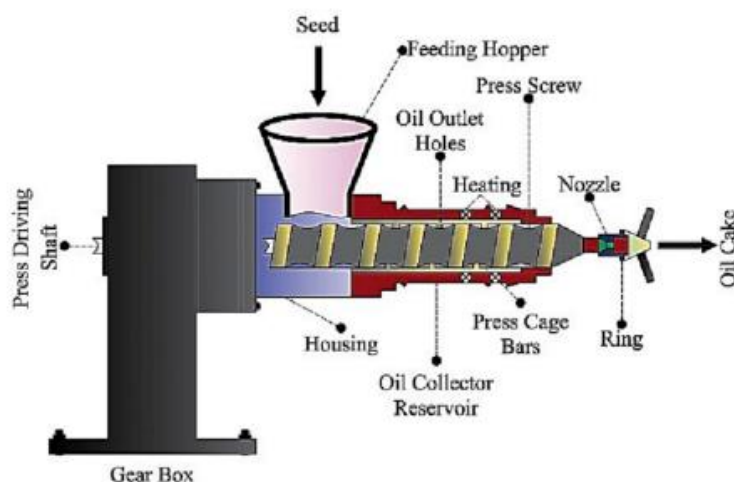


Figure 12: Mechanism of cold extraction (Deviren and Aydın, 2023).

I.2.2. Traditional extraction

First, the fruits were ground using stone grinding wheels or with a metal grinder and knead to release the maximum amount of oil. Next, to improve the oil's filtering, the paste was applied on fiber disks known as scourtins and compressed by running warm water over the disks' edges (the oil and the margine flow while the grignon remains between the scourtins). Finally, the mixture obtained was drawn into a decanter containing cold water in order to separate the oil from the water and waste by decanting (the oil rose to the surface since it is lighter than water), and the oil was collected (Figure 13).

The oils obtained by both methods were stored in opaque glass bottles labeled. They were kept cool away from light until later use.

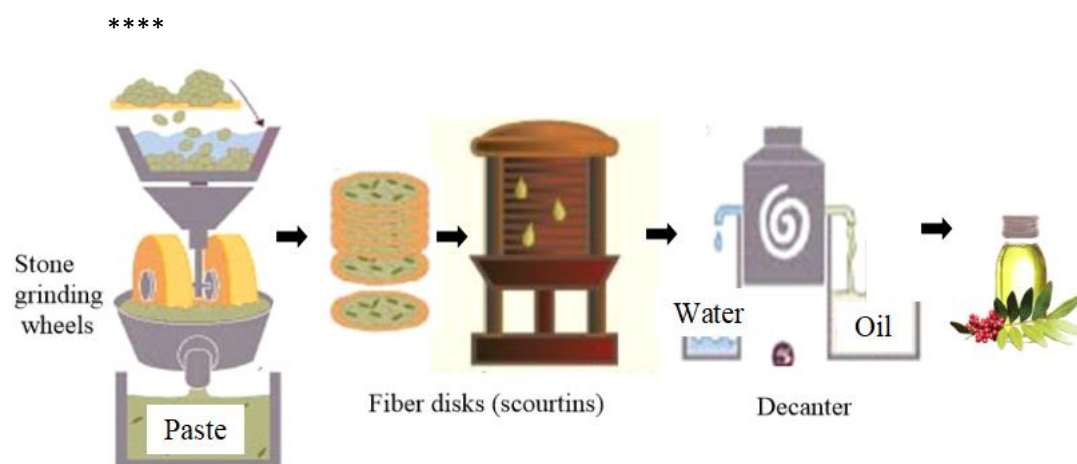


Figure 13: Mechanism of hot extraction.

II.1. Physicochemical characterization of oils

II.1.1. Yield

The following formula was used to calculate the extraction yield:

$$\text{Yield}(\%) = \frac{\text{Mass of oil extracted (g)}}{\text{Seed mass used (g)}} \times 100$$

II.1.2. Color determination

The color was evaluated by a Lovibond scale tintometer (PFX 880, Tintometer GmbH, Dortmund, Germany) in a 1-inch cell using the CIE Lab coordinates (L *, a *, b *), where L* is lightness, a* is the green-red component, and b* is the blue-yellow component (Rossi et al., 2001). The Lovibond scale is based on the color absorbance of different lenses, where Lovibond degrees are determined by comparing the color of the light transmitted through an optical path of the sample with the color of the light that comes out of the same source after passing through a series of standard color glass filters. The combination of three primary colors and neutral filters that corresponds to the absorption of the sample defines the CIE Lab coordinates (L *, a *, b *) (Ait Atmane et al., 2021).

II.1.3. Relative density at 20°C: (NF T 75-111)

It is defined as the ratio of the mass of a certain volume of oil at 20°C to the mass of an equal volume of distilled water at the same temperature (Boughendjioua and Djeddi, 2018).

$$\alpha_{20}^{20} = \frac{(m_2 - m_0)}{(m_1 - m_0)}$$

Where;

m₀: is the mass in gram of the empty pycnometre;

m₁: is the mass in gram of the water-filled pycnometre;

m₂: is the mass in gram of the oil-filled pycnometre

II.1.4. Determination of the refractive index

Refractive index (IR) is the ratio of the speed of a light in air to the speed of the same light in a substance (Ameri, 2025). The refractive index was determined by depositing a few drops of oil between the prisms of the digital refractometer (DR 201-95, Krüss Optronic, Hamburg, Germany). The temperature was set at 20 °C. The method followed is that described by ISO 6320 (2006), revised in 2017.

Procedure:

Set the temperature to 20°C; place 2 to 3 drops of oil between the refractometer prisms; the unit being calibrated beforehand with distilled water; the refractive index is determined by direct reading.

II.1.5. Determination of acid index

The acid index corresponds to the number of milligrams of potassium hydroxide used in the neutralization of free fatty acids contained in 1g of fat. The principle is based on the neutralization of fatty acids by an ethanolic solution of potassium hydroxide (Novidzro et al., 2019).

This index was determined according to the method Ca 5a-40 de l'AOCS (2017).

Procedure

2.5 g of oil is dissolved in 12.5 mL of the mixture of diethyl oxide/ethanol (v/v), and 0.5 mL of phenolphthalein 1% is added to the middle as a color indicator, then titrated, stirring, with potassium hydroxide (KOH) solution at 0.1 N, until the appearance of a persistent pink color.

The acid index is expressed as a percentage (%) of oleic acid and calculated according to the following formula:

$$IA = \frac{N \times V \times M/m}{100}$$

N: normality of potassium hydroxide,

V: volume in millilitres of the potassium hydroxide solution used,

m: mass in grams of the sample,

M: equivalent-gram of oleic acid = 282 g/mol.

II.1.6. Determination of peroxide index

The peroxide index of a fatty substance is the number of milliequivalents of active oxygen contained in 1 kilogram of product and oxidizing potassium iodide with iodine release and titration of iodine by sodium thiosulfate; this parameter estimates the degree of oxidation of oils (Novidzro et al., 2019).

The principle is based on the titration of iodine released by a solution of sodium thiosulfate $\text{Na}_2\text{S}_2\text{O}_3$. The peroxide index is measured according to the protocol recommended by the Turkish national institution (Turkish Standards Institution, 2017).

Procedure:

0.3 g of oil was weighed in a flask and mixed with 10 mL of the mixture of acetic acid/chloroform (3:2 v/v); everything is stirred. 0.5 mL of potassium iodide (KI) was added, and the mixture was stirred for 1 min and let stand for 5min away from light at a temperature of 15 to 25 °C. 10 mL of distilled water and 0.5 mL of starch solution (1 g/100 mL) (as an indicator) were added, followed by a titration of the iodine released with a solution of sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3$) at 0,002N, stirring vigorously until the color disappeared. A blank test without fat was carried out in parallel.

The peroxide index in milliequivalents of O_2/kg of sample is calculated according to the following equation:

$$\text{IP (mEq O}_2\text{/kg)} = \frac{(\text{Ve} - \text{Vb}) \times \text{N}}{\text{m}} \times 1000$$

where :

Ve : volume of Na thiosulfate to titrate the sample in milliliters,

Vb : volume of Na thiosulfate required to titrate the blanc,

m : mass in grams of the sample,

N : normality of sodium thiosulfate used in titration.

II.1.7. Determination of Saponification Index (SI) (mg KOH/g oil)

It is the number of milligrams of KOH needed to neutralize free acidity and saponify hot esters of 1 g of lipid. To determine the saponification index, we applied the method (ISO: 3657 - 2013).

Procedure:

In a flask, weigh a 2g sample, add 25 mL of potassium hydroxide ethanolic solution KOH (0.5N), connect the reflux refrigerant to the flask, place the flask on the heater, and boil gently, stirring from time to time, for 60 min. Add 0.5 mL to 1 mL of phenolphthalein solution to the hot solution, and titrate with 0.5 N HCl hydrochloric acid to remove the pink color of the indicator.

Perform a blank test also using 25 mL of KOH potassium hydroxide ethanolic solution, but omitting the test portion.

The saponification index is calculated according to the equation:

$$I_s = \frac{(V_0 - V_1) \times c \times 56.1}{m}$$

Where :

V_0 is the volume, in millilitres, of the HCl hydrochloric acid titrated solution, used to titrate the blanc;

V_1 is the volume, in millilitres, of the standard HCl solution used to titrate the sample;

c is the exact concentration, in moles per litre, of the HCl hydrochloric acid titrated solution

m is the mass, in grams, of the test sample

II.1.8. Determination of Iodine Value

The iodine index is the number of grams of iodine monochloride fixed per 100 g of fat. It measures the degree of unsaturation of a fat (Novidzro et al., 2019). This index was determined by the method of iodometric titration according to the protocol of the Turkish national institution (Turkish Standards Institution, 2018).

Procedure:

Weigh a test portion of 0.3 g of fat in a flask and add 15 ml of carbon tetrachloride and 25 ml of Hanus reagent; shake the flask gently and let the mixture rest in the dark for one hour. Then add 20 ml of 10% KI and 150 ml of distilled water; shake and titrate the mixture with sodium thiosulfate solution ($\text{Na}_2\text{S}_2\text{O}_3$) (0.1N) in the presence of some drops of starch (1%).

A blank test without oil shall be carried out in parallel.

The iodine number is calculated by the following equation:

$$\text{II [g of I}_2\text{/100g of oil]} = 12.69 \times \frac{V_0 - V}{m} \times N$$

V_0 : is the volume in ml of sodium thiosulfate to titrate the blanc,

V : is the volume in ml to titrate the sample,

N : is the normality of the sodium thiosulfate solution used,

m : is the test sample in grams

II.1.9. Determination of conjugated dienes (k232)

Conjugated dienes are defined by two double bonds separated by a simple bond in lipids; their presence indicates an autooxidation of lipids (Corongiu and Banni, 1994). The AOCS Ti 1a-64 method (AOCS, 2017) was used to determine conjugated dienes (k232).

Procedure:

1.25 mg of oil was diluted in 25 ml of isooctane, followed by gentle agitation. Then put in the dark for 15min, after absorbance is read at 232nm against a blanc containing isooctane.

The value of K232 is expressed in% and calculated according to the following formula.

$$\text{K232} = \frac{0.84 \times (A_e - A_0)}{b \times c}$$

where :

A_e : absorbance of the sample,

A_0 : correction factor (0.07),

b : tank width (1cm),

c : sample concentration (g/l)

II.2. Phytochemical characterisation

II.2.1. Fatty Acid Content by GC

The AOCS method (2017) was used to prepare fatty acid methyl esters. 100 mg of oil was weighed in a centrifuge tube, 2.5 mL of n-hexane and 0.5 mL of potassium hydroxide methanol solution (2N) were added, and the tube was vortexed for 1 min, and centrifuged at 6000 rpm for 10 min. The upper phase was transferred to a CG vial where 1 μ L was injected; the Agilent 6890 series GC equipped with a fused silica capillary column SP-2380 (60 m $\times$ 0.25 mm $\times$ 0.2 μ m; Supelco, Bellefonte, PA) and a flame ionization detector (FID) was used.

The following operating conditions were used: the split ratio was 1:20. The GC oven temperature was maintained at 120°C for 1 min then increased to 240°C at a rate of 6°C/min, and finally maintained at 240°C for 15 min. Injector and detector temperatures were 250°C. A combination of dry air and hydrogen was used as carrier gas at a flow rate of 1 mL/min.

The fatty acids were identified by comparing the retention times of their peaks with those of pure standards analyzed under the same conditions, quantified using the area of the relative peaks expressed as a percentage (%).

II.2.2. Determination of total polyphenols

The total polyphenol content was determined by the Folin-Ciocalteu reagent colorimetric method with slight modification (Hrncirik and Fritsche, 2004). The principle is based on the reduction of the Folin-Ciocalteu reagent in the presence of total phenols. The products indicating the reduction are of a blue color that has a wide absorbance with a maximum at 760 nm. The intensity of light at this wavelength is proportional to the concentration of phenols (Cicco et al., 2009).

In brief, 0.5g of oil is dissolved in 10 mL of methanol, stirred for 30s and centrifuged at 6000 rpm for 20 minutes, and then the methanolic phase is recovered. 1 mL of methanolic extract is introduced into a volumetric flask of 25 mL, and 5 mL of distilled water and 0.5 mL of Folin-Ciocalteu reagent are added and incubated in the dark for 5 min. After that, 1 mL of Na₂CO₃ solution (35% w/v) is added. The volume was increased to 25 mL with distilled water

and then incubated in the dark for 2 h. The absorbance was read against a blank at 725 nm using a microplate spectrophotometer (Thermo Scientific Multiskan Go, USA).

The amount of total polyphenols is expressed as milligrams of gallic acid equivalents per 100g oil (mg GAE/100g of oil), referring to a calibration curve ($R^2 = 0.993$) made with gallic acid under the same conditions (Annex).

II.2.3. Analysis of the polyphenolic profile by HPLC-DAD

The phenolic compounds of the oils were analyzed according to the standard method of the International Olive Council (2017) using high performance liquid chromatography.

In a centrifuge tube, 2 g of oil was dissolved in 5 mL of methanol/ water solution (80%; v/ v). The tube is then vortexed for 1 min then placed in an ultrasonic bath for 15 min before being centrifuged at 5000 rpm for 25 min. The supernatant obtained is filtered by a PTFE syringe filter (0.45 μ m). 20 μ L of filtrate is injected into the high performance liquid chromatography system (Agilent technologies, Palo Alto, CA, USA) equipped with a Licrospher RP18-5 column (250 mm x 4.0 mm, 5 μ m), (Hichrom, Reading, UK) and a photodiode array detector (DAD) with detection at 280 nm.

The following operating conditions were used to identify phenolic compounds: Mobile phase: solvent A (0.2% orthophosphoric acid in water), solvent B (methanol) and solvent C (acetonitrile), the program gradient is: 0 min (96% A, 2% B ,and 2% C), 40 min (50% A, 25% B ,and 25% C), 45 min (40% A, 30% B ,and 30% C), 60 min (0% A, 50% B ,and 50% C), 70 min (0% A, 50% B ,and 50% C), 72 min (96% A, 2% B ,and 2% C), 82 min (96% A, 2% B ,and 2% C).

The identification of phenolic compounds was obtained by comparing their retention time with those of the external pure standards; their quantification is carried out by referring to the calibration curve of each standard. The results are expressed in mg/100g of oil.

II.2.4. Identification of tocopherols and tocotrienols by HPLC-DAD

Tocopherols and tocotrienols of *Pistacia lentiscus* oils were analyzed using the IUPAC standard method (1992).

An amount of 0.4 g of oil was diluted with a solution of isopropyl alcohol/acetic acid/hexane (0.2:0.8:99; v/v). After complete dissolution, the mixture is filtered through a

0.25 μm PTFE syringe filter and then transferred to amber vial; and 20 μL of filtrate is injected into the high performance liquid chromatography system (1260 Infinity) equipped with a diode array detector (DAD) (Agilent Technologies, Waldbronn, Germany) operating at 292 nm.

The following operating conditions were used to separate the tocopherols: Hypersil Column H5 (250 mm x 4.6 mm, 5 μm , Hichrom, Reading, UK); temperature: 20 $^{\circ}\text{C}$; mobile phase: isopropyl alcohol, acetic acid, and hexane (0.2:0.8:99; v/v).

Tocopherols and tocotrienols are identified using the retention times of the external standards and quantified by reference to the calibration curves (annexe) determined for α -tocopherol, α -tocotrienol, β -tocopherol, β -tocotrienol, δ -tocopherol, δ -tocotrienol, γ -tocopherol and γ -tocotrienol. Results are expressed as mg/kg of oil.

II.3. Evaluation of anti-radical activity (DPPH)

DPPH $\cdot$ (2,2-phenyl-1-picryl hydrazyl) is a free radical of violet color that is reduced in the presence of proton donors to DPPH-H (2,2-phenyl-1-picryl hydrazine) of yellow color. The intensity of staining is inversely proportional to the antiradical activity (Benkhaled, 2018).

The DPPH radical scavenging experiment developed by Rotondi et al. (2004) was used to assess the overall antioxidant capability of the oils. 0.5 g of oil is weighed and mixed with 10 ml of methanol under gentle agitation for 30 seconds, then centrifuged for 20 min at 6000 rpm. A volume of 0.2 ml of the methanolic phase was mixed with 3.8 ml of the methanolic solution of DPPH (100 μM). After incubation in the dark for 15 minutes at 25 $^{\circ}\text{C}$, absorbance was measured at 517 nm against a blank test. A Trolox calibration curve ($R^2 = 0.989$) was used (annex), and the results were expressed as millimoles of Trolox equivalent per 100g of oil (mM TE/100g of oil).

II.4. Antimicrobial activity

The evaluation of antimicrobial activity was carried out against five strains of pathogenic bacteria and one yeast, obtained from the Microbiology laboratory of the Faculty of Science, University of Boumerdes, namely: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus cereus* ATCC 14579, *Pseudomonas aeruginosa* ATCC 27853 and *Listeria monocytogene* ATCC 7644, against one yeast: *Candida albicans* 27/4, and against six

fungus strains isolated in the microbiology laboratory, ENS, Kouba, Algiers: *Umbelopsis ramanniana* NRRL 1829, *Fusarium culmorum* NRRL.1829, *Aspergillus niger*, *Aspergillus flavus* NRRL 3251, *Aspergillus carbonarius* M333, and *Aspergillus parasiticus* CBS 100926. To have young cultures, bacterial strains were grown on Muller-Hinton agar and fungi were grown on Sabouraud dextrose agar. All microbial strains were incubated at 37°C for 24 hours.

The disc diffusion method described by (Ksouri et al., 2017) was used. Microbial cultures were suspended in a sterile saline solution (0.9% NaCl); cell density was adjusted to 0.5 McFarland for bacterial strains and yeast and 0.4 for fungal suspensions. Twenty milliliters of melted agar mixture were poured into sterile petri dishes. A suspension of bacteria and fungi (100 µL) was distributed on the plates containing the nutrient agar, and then the plates were dried aseptically for 2 hours at room temperature. Sterile paper disks (6 mm) were impregnated with 10 µL of oil and placed on the inoculated surface. Prior to incubation, the petri dishes were incubated at +4°C for 1 to 2 hours to allow the diffusion of the oils present in the discs. Finally, they were incubated for 18-24 h at 37°C for bacteria and 48-72 h at 30°C for yeasts and fungi. The antimicrobial activity was evaluated by measuring the inhibition zone in millimeters (without taking into account the disc diameter). The tests were carried out in triplicate.

Antibacterial activity is classified as follows: (Ponce et al., 2003)

Table 5: Scale of germs sensitivity.

Diameter of the inhibition zone (mm)	Gender sensitivity
0	Resistant
< à 8 mm	Not sensitive
between 9 and 14 mm	Sensitive
between 15 and 19 mm	Very sensitive
> 20 mm	Extremely sensitive

II.5. Wound healing activity

The aim of this study is to evaluate the effectiveness of vegetable oil extracted from *Pistacia lentiscus* L. fruits for wound healing in albino rats.

II.5.1. Animals and experimental lots

All animal experiments protocols were performed according to the International Council for Laboratory Animal Science (2024) and approved by the Ethical Committee of Directorate General for Scientific Research and Technological Development at Algerian Ministry of Higher Education and Scientific Research (PRFU D01N01UN280120200002).

Wistar strain albino rats served as an experimental model. Healthy rats (150-200 g) were purchased from Pasteur Institute of Algeria. Each animal was placed in individual cages and fed *ad libitum*. The rats were acclimatized to laboratory conditions for 7 days.

The weighed and marked rats were divided into 4 groups of 5 rats each as follows: Untreated group (UT group), Cicatryl-treated group (CIC group), HLCO-treated group and HLHO-treated group.

II.5.2. Induction of the skin wound

Before treatment, the back of each rat was shaved with an electric clipper. The rats were anesthetized with an intraperitoneal injection of ketamine (90 mg/kg) xylazine (10 mg/kg) (Mashreghi et al., 2013). A circle of approximately 2.5 cm in diameter was drawn on the skin of the lumbar region, quickly cleaned with 70% ethanol (v/v) and then excised. The animals were placed in individual cages with clean litters and excisional wounds were immediately treated (Draize, 1944).

II.5.3. Application of treatments

The different treatments (CIC, HLCO and HLHO) were applied once a day topically until healing, at a rate of 0.5 g per rat for 18 days (Pipelzadeh et al., 2003).

The development of the excision wounds was monitored every 3 days by measuring their dimensions. This was done by tracing the wounds on transparent paper and measuring the subsequent growth on graphic paper. The percentage of the evolution of wound contraction was calculated as follows :

$$\% \text{ wound contraction} = \frac{(\text{initial wound size} - \text{specific day wound size})}{\text{initial wound size}} \times 100$$

II.5.4. Histopathological analysis of wounds

After 18 days of treatment, the rats were sacrificed and biopsies of the skin surrounding the treated wounds were performed. The histopathological analysis was carried out in the anatomopathology laboratory of ISSAD HASSANI hospital; the steps are shown in figure 14.

The skin was placed in embedding cassettes and fixed in 10% (V/V) buffered formaldehyde solution for 72 h "fixing stage" (which allowed for the immobilization of tissue and cellular components). Next, the cassettes were dehydrated by passing them through ethanol baths at increasing concentrations of 70°, 75°, 80°, 85°, 90°, 95°, and 100° in a dehydration automaton (circulator). The purpose of this passage was to remove any remaining fixator residue, and water was replaced with toluene in the lightening step.

The samples were then impregnated in two baths of molten paraffin at 70°C (the impregnation step) and then put into paraffin-filled molds (the coating step). Following the paraffin's solidification, the tissue blocks were chilled, and a microtome was used to cut the tissue into slices that were 5 µm thick.

After the slices are obtained, they are spread out on slides impregnated in a water bath and dried in an oven at 40-45 °C for 24 hours. The sections were then passed through toluene and ethanol baths at decreasing concentrations of 100°, 90°, 70°, and 50° for rehydration, and then they were colored using hematoxylin-eosin (Marque, 2010) by impregnating them in various solutions: xylene (30 minutes), water (10 minutes), ethanol (10 minutes), hematoxylin (5 minutes), wash running water, eosin (3 minutes), and two consecutive washings with water.

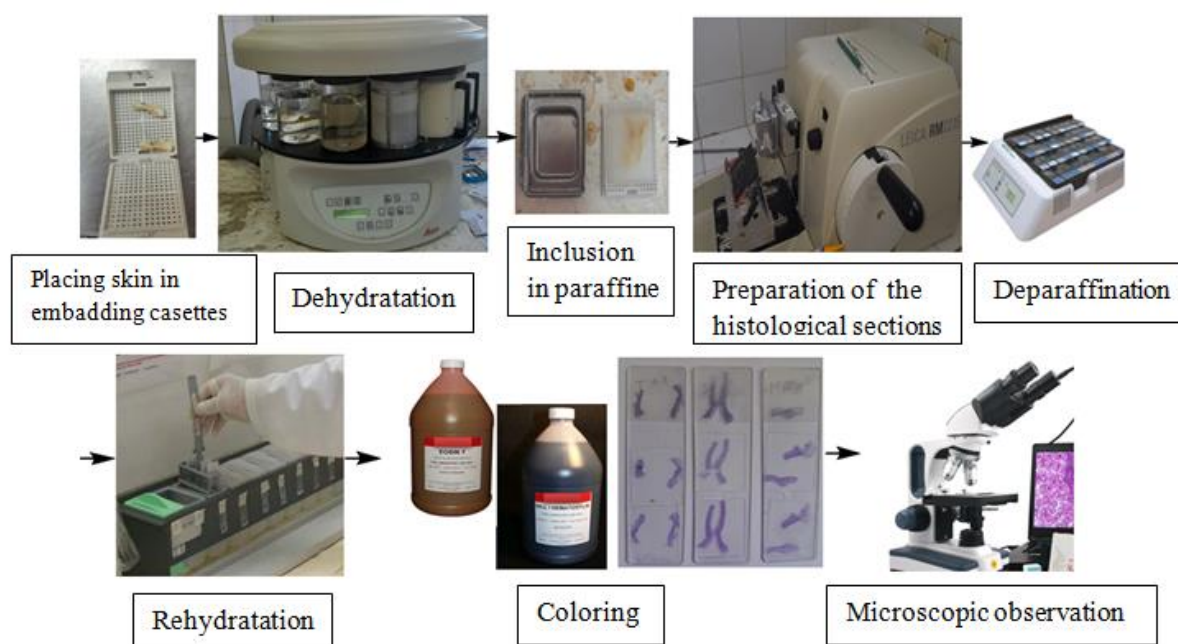


Figure 14: Histopathological analysis steps.

II.5.5. Observation and microscopic analysis

The prepared sections were photomicrographed (Optika B-350 microscope equipped with OPTIKAM Pro 8LT camera) and analyzed using the image processing software, Optika™ Vision Pro (Optika Microscopes, Italy). Analyses were performed to confirm the presence of inflammatory cell, collagen and angiogenesis levels in the tissues on day 18 post-injury.

The observations were conducted by Professor Oudjida Faiza, a professor at ISSAD HASSANI Hospital.

II.5.6. Study of skin irritation

The skin irritation test was used in accordance with the Organization for Economic Co-operation and Development (OECD) guidelines 404 (OECD, 2015). HLHO and HLCO were applied topically on the back of the animals at an amount of 0.5 mL per rat. The animals were observed for mortality and any toxic or deleterious effects, with particular attention paid to the first 4 hours, then once a day for a period of 14 days following topical application. At the application sites, the skin was observed for signs of erythema, edema and local injury. The rats were weighed before and during treatment to assess the effect of the experimental treatments on body weight.

II.6. Molecular docking

Inflammation is a complex physiological reaction that serves as a defensive mechanism against injury, infection, and tissue stress (Middha et al., 2016, Belakredar et al., 2024). Acute inflammation follows an injury, manifests quickly, and usually resolves within a few days. The main goals of acute inflammation are to eliminate harmful substances and start tissue repair mostly through the actions of immune cells such as macrophages and NK cells by activating diverse molecular signaling pathways (Aziz et al., 2018). When inflammation lasts more than six weeks, it becomes chronic. Chronic inflammation must be treated in order to prevent major issues such as tissue damage and fibrosis from developing (Ekowati et al., 2023). Therefore, regulating inflammatory responses is necessary to prevent immune cells from inflicting more tissue damage and to stop the progression of disorders linked to inflammation. These factors make anti-inflammatory agents extremely desirable (Aziz et al., 2018).

Cyclooxygenase (COX), an endogenous enzyme, converts arachidonic acid into prostanoids (prostaglandins, prostacyclins, and thromboxanes), which are all implicated in the

inflammatory response (Tendulkar and Mahajan, 2014, Middha et al., 2016). Two isozymes of COX exist: Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2). COX-2 is present at sites of inflammation, while COX-1 is homeostatic and expressed in various tissues, such as the kidney, platelets, and digestive system (Bouaziz-Terrachet et al., 2010). By suppressing COX-1 and COX-2, nonsteroidal anti-inflammatory drugs (NSAIDs) prevent the synthesis of prostaglandins. The majority of these medications have adverse effects at the gastrointestinal system (bleeding, mucosal damage) and less commonly on the renal level. These medications induce their negative side effects by inhibiting COX-1 and their beneficial effects by inhibiting COX-2. Therefore, selectively inhibiting COX-2 without harming the homeostatic one could avoid the adverse effects of currently available NSAIDs (Bouaziz-Terrachet et al., 2010, Tendulkar and Mahajan, 2014, Afroz et al., 2019).

Molecular docking is a novel computational approach that has gained prominence in medicinal chemistry with the expansion of databases such as PDB, PubChem, ChEMBL, and the Drug Bank, as well as new data from traditional in vivo and in vitro research (Wishart et al., 2006).

Protein-ligand docking is an important application of molecular docking. This method is easier to set up, quicker, and far less expensive than experimental screening as it simulates the binding affinities of several ligands for a certain therapeutic target (Afroz et al., 2019). These methods are now essential and vital parts of many drug development initiatives. The current work aimed to assess the binding of phenolic compounds found in lentisk oil to COX-2 in order to investigate their COX-2 inhibitory action, which could facilitate the development of stronger anti-inflammatory drugs in the future.

II.6.1. Software used in this study

Molecular docking studies were carried out using PyRx 0.8, Molecular Graphics Laboratory (MGL) tools, and BIOVIA Discovery Studio 2021 client Visualizer v21.1.0. These softwares were downloaded respectively from www.pyrx.sourceforge.io, www.scripps.edu, and www.discover.3ds.com.

II.6.2. Preparation of ligand

The detected phenolic compounds of lentisk oil identified using HPLC were employed in this study. Two-dimensional (2D) and three dimensional (3D) structures of these compounds were drawn and optimized using BIOVIA Discovery Studio 2021 client Visualizer v21.1.0.

II.6.3. Preparation of protein

The protein used in this study corresponds to the crystal structure of COX-2. This protein is complexed with a non-selective inhibitor, flurbiprofen, and it was downloaded from the Protein Data Bank (PDB ID: 3pgh) figure 15. After removing the ligand and water molecules, all missing hydrogens were added.

The active site was taken using a grid box with the coordinates X: 26.629, Y: 22.503, and Z: 17.855, so that the amino acid residues (namely Val116, Val349, Arg120, Ala527, Leu352, Leu359, and Leu531) could be included. After the assignment of Gasteiger charges, nonpolar hydrogens were merged with their corresponding carbons, and finally pdbqt formats of the protein structure were downloaded.

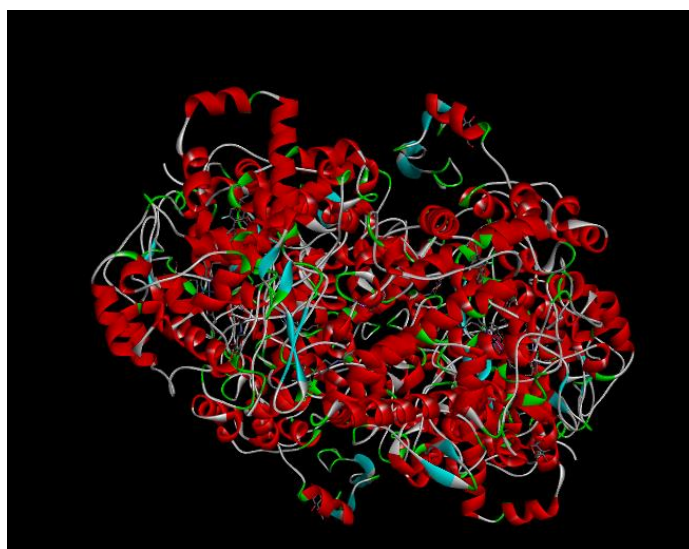


Figure 15: 3D structure of cyclooxygenase-2 (3pgh).

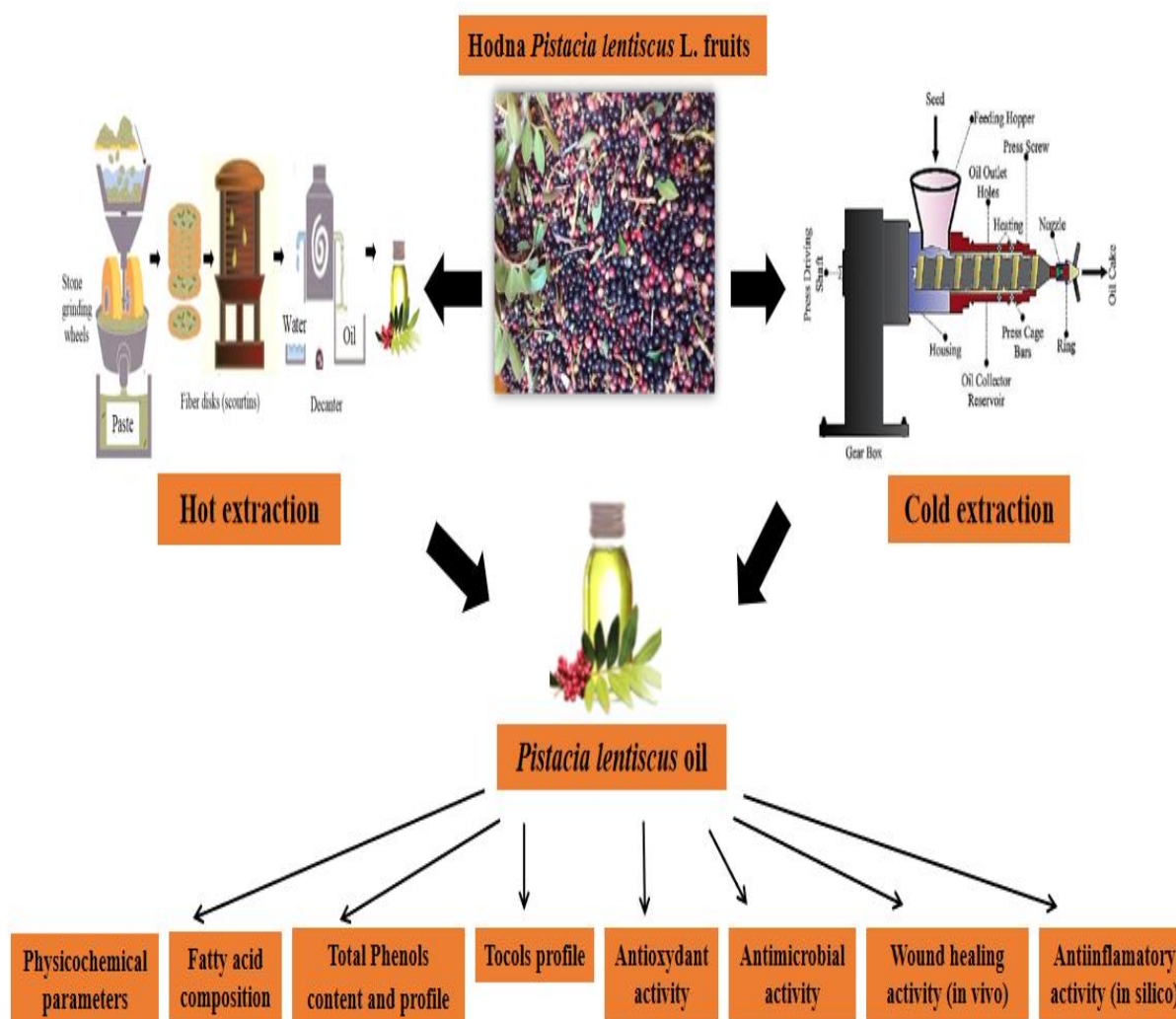
II.6.4. Simulation studies

PyRX software was then used to investigate the interaction between all of the phenolic compounds found in our oils and COX-2. The results were verified by the BIOVIA Discovery Studio 2021 client Visualizer v21.1.0. Amino acid residues, hydrogen bonds, other interactions, and energy binding created by interactions are all included in the analysis. The minus value shows that the binding of the ligand to the target protein is easier because it requires less energy to bind. A low docking score indicates that the ligand has a significant inhibitory effect on the receptor. Upon completion of docking, the optimal ligand conformation was examined for its binding interactions.

II-7- Statistical Analysis

The research has a completely randomized (CR) design, with the single factor being oil extraction type. SPSS Statistics 27 (SPSS Inc., Chicago, USA) was used for the statistical analysis. An independent samples *t*-test was used to determine the statistical differences between the means of different physicochemical, phytochemical parameters and antioxidant activity. One-way ANOVA was used to determine differences between treatments, followed by Tukey post hoc test. The significance was set at 0.05.

Graphical design



Results and discussion

Results and discussion

I. Physicochemical parameters

The Physicochemical properties of lentisk seed oils, extracted by cold extraction (pressing method) and hot extraction (traditional method), are shown in Table 6.

The following physico-chemical parameters were used to determine oil quality: color, density, refractive index, free fatty acids, peroxide index, conjugated dienes, iodine value and saponification number. These parameters demonstrated differences between the two techniques. It is worth mentioning that all of the fruits were obtained from the same sub-arid region (El Hauran) using two distinct methods, and all of the seeds and extracted oils were kept in the same manner and under identical conditions. For this reason, the differences between the two oils (HLCO and HLHO) are solely due to their extraction processes.

Table 06: Physicochemical properties of *P. lentiscus* seed oils extracted by cold extraction (HLCO) and hot extraction (HLHO).

Parameters	HLHO	HLCO	<i>p</i> -value*
Yield (%)	5.2 ± 0.52	15.3 ± 0.71	0.0000***
Color Visual perception	Yellow brown	Yellow brown	-
<i>L</i> *	38.50 ± 0.03	67.49 ± 0.01	0.0000***
<i>a</i> *	1.65 ± 0.00	3.03 ± 0.00	0.0000***
<i>b</i> *	65.52 ± 0.07	110.25 ± 0.12	0.000***
Density (g/mL)	0.89 ± 0.01	0.91 ± 0.01	0.0705
Refractive index	1.466 ± 0.00	1.470 ± 0.00	0.2455
Free fatty acidity (% oleic acid)	0.33 ± 0.01	0.43 ± 0.01	0.0000***
Saponification number (mg KOH/g oil)	146.50 ± 0.32	111.41 ± 0.00	0.0000***
Iodine value (g I₂/100g oil)	76.74 ± 2.83	109.58 ± 4.41	0.0000***
Peroxide value (mEq O₂/kg)	3.15 ± 0.09	1.31 ± 0.02	0.0000***

Conjugated dienes (K₂₃₂) (%)	0.52 ± 0.08	0.66 ± 0.06	0.0684
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Values are average of triplicate analyses ± SD

Significance of differences (*t*-test, *P* < 0.05): **P* < 0.05, ***P* < 0.01, ****P* < 0.001

I.1. Yield of extraction

Regarding the influence of the extraction method, the highest oil yield ($15.3 \pm 0.23\%$) was achieved with cold pressing method, while the minimum value was obtained with the traditional hot method ($5.2 \pm 0.18\%$). The yield obtained by cold pressing method is three times higher than the traditional hot method. These findings confirmed that the extraction method affect significantly the oil yields.

Haouli et al. (2015) found similar results, reaching 6% using the traditional method, while Djebari et al. (2020) found 16.66% for vegetable oil extracted traditionnaly from fruits harvested in Bejaia.

Gaout et al. (2012) reported that the oil yields produced by cold pressing method from seeds gathered from different locations of Tunisia were different. The cold pressed oil harvested in Guelma (Northeastern Algeria) reached a yield of 31% which is higher than the yield recorded in our study (Hamdi et al., 2023). Also the cold pressed oil harvested from Beja (Northwest of Tunisia) recorded a high yield (22.71%) (Ben Ameur et al., 2024).

Our findings are consistent with previous investigations that shown that cold pressing method increases yield as compared to traditional methods. At an industrial scale, vegetable seed oil is preferably extracted by continuous screw pressing (Singh and Bargale, 2000).

I.2. Color

Color results are expressed as L^* , a^* , b^* , where L^* is lightness, a^* is the green–red component, and b^* the blue–yellow component (Rossi et al., 2001). The color analysis (Table 6) shows clearly that all the color parameters of HLCO are significantly superior to those of HLHO ($p < 0.05$). The color parameters (L^* , a^* , and b^*) of HLHO and HLCO were: L^* ranged between 38.5 ± 0.03 and 67.49 ± 0.01 , a^* varied from 1.65 ± 0.00 to 3.03 ± 0.00 , and b^* was between 65.52 ± 0.07 and 110.25 ± 0.12 , respectively. The obtained oils have a yellow brown color, this color is owed to the high value of parameter b^* in both oils which is higher than L^* and a^* values. Nevertheless, the higher b^* value of HLCO suggests a more intense yellow color, indicating increases carotenoid content (Rotondi et al., 2004, Chouaibi et al.,

2020). Certain carotenoids are potent antioxidants (precursors of vitamin A) that prevent serious human ailments such as cardiovascular and skin diseases (Voutilainen et al., 2006, Bernstein, 2002) and cancer (Nishino et al., 2002). Their adequate presence in the oil prevents photo-oxidation and maintains the oil's quality while it is being stored (Lazzez et al., 2006). It should be noted that the low values of a^* (greenness) for both mastic seed oils might be attributed to the lack of chlorophylls or any other green pigment. Lastly, it should be mentioned that many factors, including maturation stage, extraction method, and storage conditions, affect the pigment content of fruits (Ramadan et al., 2003).

I.3. Density

The density of oils is mostly determined by their chemical composition, which provides information on the characteristics of fatty acids, such as chain length, degree of unsaturation, and functional groups throughout the carbon chain (Maameri-Habibatni, 2014). Our study revealed that there are no significant differences between the samples density (Table 6). The density values were 0.89 for HLHO and 0.91 for HLCO, which appeared to be similar to the findings of Boukeloua et al. (2012), Maameri-Habibatni (2014) and Djerrou (2014) as 0.918, 0.91 and 0.919, respectively. However, the density values for the oil (1.02) extracted using the cold pressing method reported by Brahmi et al. (2020) and the oil (1.3) extracted using the soxhlet method reported by Boudiaf et al. (2018) were higher than our results.

I.4. Refractive index

Nearly identical refractive index values are found for the oils (Table 6) (1.469 ± 0.00 for HLHO and 1.47 ± 0.00 for HLCO) and concur with those reported in the literature as 1.466, 1.468, and 1.463 by Djerrou (2014), Brahmi et al. (2020) and Kechidi et al. (2020) respectively. These values are identical to those of common vegetable oils. Refractive index is dependent on both the oil's composition and temperature, just like density. The length of the fatty acid chain and its degree of unsaturation are revealed by the refractive index of oils (Shahidi and Zhong, 2005), as a matter of fact, it increases with the presence and the degree of unsaturation of secondary functions on the fatty acid chain (Boukeloua et al., 2012).

I.5. Free fatty acid

Acidity is related to the amount of free fatty acids (FFA) which result from the hydrolytic reactions of triglycerides. FFA is one of the most important physicochemical factors in oil industry that provides information on the quality of conservation of edible oil

(Kandji, 2001). The FFA values of our oils (Table 6) obtained from the hot ($0.33 \pm 0.001\%$) and cold extractions ($0.43 \pm 0.001\%$) were notably lower than vegetable oils reported in previous researches indicating a low degree of hydrolysis of the oils. A significant difference ($P < 0.05$) was noticed between the acidity values of the two oils. The oils of *P. lentiscus* from the Hodna sub-arid region obtained by both extraction methods had substantially lower acidity levels than any other research. Relatively high acidity values were reported for *P. lentiscus* oil of fruits harvested in the east of Algeria. The acidity values obtained from Skikda region were 2.27% (Boukeloua et al., 2012), and 3.1% (Azizi et al., 2022). In addition, the acidity value of lentisk oils collected from Annaba, Ain Khia, Bougous, Bouhadjar, Guelma and Souk Ahras were 5.72%, 2.24%, 8.22%, 8.36%, 8.25% and 4.52%, respectively (Beldi et al., 2020). Likewise, the acidity value of oil harvested in Collo found by Boudiaf et al. (2018) was 2.7 % and Bensalem (2015) found 2.05 % for lentisk oil collected from Jijel. The values recorded in middle region of Algeria were 7.7 mg KOH/g in Tipaza (Charef et al., 2008) and 3.52 mg KOH /g of oil (Brahmi et al., 2020). In the western region of Algeria (Ain defla), the acidity value found by Kechidi et al. (2020) was 14.41%.

The acidity values of *lentiscus* oils from 12 localities of Northern Algeria ranged from 1.68% for locality of Lakhdaria and 3.17% for locality of Ain Ben Beida (Chemani et al., 2022). Interestingly, these 12 oils' acidity is likewise significantly higher than the acid values found in our study.

Internationally, the acidity values of lentisk seed oil were higher than our findings, Ait Mohand et al. (2020) recorded 2.61% for Moroccan oil. This value is at least six times higher than of our study. Likewise, Bouyahya et al. (2018), also from Morocco, revealed a high acid value (4%). Nevertheless, the acidity obtained of the Tunisian oils was 3.02% (Khedir et al., 2018) and 4.14% (Karoui et al., 2020). In Italy, the FFA value was 3.48% (Siano et al., 2020). Obviously, these values are higher than those recorded in this study more than ten times.

An increase in FFA level in an oil or fat sample signifies the hydrolysis of triglycerides. The lipase enzyme promotes this reaction, which is a sign of inappropriate processing and storage conditions (high temperature and relative humidity, tissue damage). Poor harvesting and milling techniques, however, can also have an impact on free fatty acid levels. The acidity of fresh lentisk fruits can potentially increase if they remain too long before being ground or dried (Brahmi et al., 2020).

I.6. Peroxide value

Peroxide value (PV) is a highly reliable indicator of freshness and oil quality (Codex Alimentarius Commission (1stedn), 1982), it measures the amount of peroxides in the oil and, consequently, the degree of oil oxidation (Tchiégang and Aissatou, 2004). Determined by measuring released iodine from potassium iodide, PV indicates the extent of rancidity among fatty acids during storage, thing which reflect the quality and stability of oils and fats (Zahir et al., 2017). It is apparent that a high PV in vegetable oils indicates overheating or inadequate storage conditions.

The PVs of the two oils in this investigation (Table 6) were in accordance with standards and they were below the maximum limit of 15 mEq O₂/kg for virgin and cold-pressed oils defined by Codex Alimentarius (2023). Furthermore, we noticed there was a high significant difference ($p < 0.05$) between the two oils; the value obtained in HLHO (3.15 ± 0.09 mEq O₂/Kg) being at least twice as high as with HLCO (1.31 ± 0.02 mEq O₂/Kg). The combined impacts of water and the high temperature during the extraction process might account for the high value in hot extracted oil.

Previous studies conducted on lentisk oil from different regions showed varied PV results. For instance, oil from Skikda aligned closely with HLCO, registering PVs of 1.12 mEq O₂/Kg (Boukeloua et al., 2012) and 1.6 mEq O₂/Kg (Azizi et al., 2022), While high value (10 mEq O₂/Kg) was noted for the same region by Djerrou (2014) and (8.56 meqO₂/kg) for oil harvested in Bejaia (Djebari et al., 2020). However, in the west of Algeria (Ain defla), Kechidi et al. (2020) recorded a PV of 6 mEq O₂/Kg. In Tunisia Karoui et al. (2020) found a low PV (1.92 mEq O₂/Kg). In Italy, high values were found by Siano et al. (2020) for oils extracted over various years: 4 mEq O₂/Kg in 2015; 12 mEq O₂/Kg in 2016; 8 mEq O₂/Kg in 2017 and 5 mEq O₂/Kg in 2018.

Our lentisk oils exhibited the lowest acid values (0.33 and 0.43%) and peroxide values (1.31 and 3.15 mEq O₂/Kg). Based on our study, these oils, could be considered fresh oils, possessing good storage stability and high edibility.

I.7. Saponification number

The saponification number (SN) is a significant indicator of oil quality, providing insight into the average molecular weight of all fatty acids, whether esterified or free. It is defined as the amount of alkali (expressed as mg KOH/g sample) required to saponify a defined amount

of sample. SN is reliant on the length of the fatty acyl chains from triacylglycerols since the quantity (moles) of base reacted is stoichiometrically equal to the amount (moles) of fatty acyl chains present in 1 g of oil/fat. Therefore, SN is inversely proportional to the molecular weight of the fatty acids (Xu et al., 2018). In this study, SN values determined for HLCO (111.41 mg of KOH/g) and for HLHO (146.50 mg of KOH/g) remain within the international Oil Council standards (IOC). However, the analysis of variance showed high significant differences among both oils for $p < 0.05$ (Table 6). Similar results were found by Beldi et al. (2020), for oils extracted traditionally from Bouhadjar (144.52 mg of KOH/g) and Bougous (117.76 mg of KOH/g), and by Charef et al. (2008) for oil extracted from Tipaza (147.8 mg of KOH/g). For Moroccan oils; Bouyahya et al. (2018) reported an average SN of 140.00 mg. Beldi et al. (2020) recorded high amounts for oils gathered from Souk Ahras (182.44 mg of KOH/g), Guelma (192.15 mg of KOH/g) and Annaba (193.4 mg of KOH/g). Similarly to Djebari et al. (2020) for oil collected from Bejaia (190.6 ± 1.34 mg of KOH/g). A very high SN of mastic seed oil from Ain defla was revealed by Kechidi et al. (2020), which was 269.28 mg of KOH/g. Similarly, for Tunisian oils Karoui et al. (2020) reported a high SN (189.12 mg of KOH/g). High values of SN demonstrate the richness of the oils in C16 and C18 fatty acids (Sbihi et al., 2013). The SN values found in this study suggest that the mastic oils from Hodna region are intended for consumption rather than the production of soap.

I.8. Iodine value

The degree of oxidation of edible oils is determined by measuring the iodine value (IV) which indicates the degree of unsaturation of the fatty acids contained in the oil, the reason why food safety officials and industry utilize this value as an authenticating tool. Higher values of iodine signify increased reactivity, lesser stability, and higher vulnerability to oxidation and rancidity and softer consistency (Flores et al., 2021). The extraction method significantly ($p < 0.05$) influenced this value where we noticed 76.74 g/100g for HLHO and 109.58 g/100g for HLCO (Table 6). HLHO have a lower IV than HLCO making it less oxidizing. Our results are similar to those of Charef et al. (2008); 109.0 g/100g for red seeds and 87.3 g/100g for black seeds harvested in Tipaza. Lower iodine values than our findings were recorded for lentisk oils extracted traditionally from different eastern regions by Bensalem (2015) such as Jijel (41.314 g/100g), Skikda (44.678 g/100g) and Guelma (44.729 g/100g). However, in Tunisia the IV of the cold pressed lentisk seed oils, was much higher than our results and ranged from 136.2 to 143.1 g/100g (Gaout, 2012). According to

Vaitilingom (2007), oils may be considered mono-unsaturated if IV is between 50 to 100 g/100g and may be considered poly-unsaturated if IV is from 100 to 150 g/100g.

I.9. Conjugated diène (K232)

No significant difference at $p < 0.05$ was revealed between K232 values for the two oils. The highest K232 value ($0.66 \pm 0.00\%$) was attributed to HLCO and the lowest value $0.52 \pm 0.00\%$ for HLHO (Table 6). These values are almost five times lower than the maximum values allowed for K232 which are 2.50 for extra virgin olive oils and 2.60 for virgin olive oil (ÖĞÜTÇÜ and Yilmaz, 2009). The K232 extinction values of *lentiscus* oil found herein are different from those found by other authors, our results are considerably lower than those reported in Tunisia by Karoui et al. (2020) and Khedir et al. (2018) which were 2.13% and 6.856%, respectively. In Morocco, the K232 values of oils extracted at different stages of maturity, green/red, red and black seeds, were higher than our values and found respectively 1.74, 1.75 and 5.03% (Ait Mohand et al., 2020); while, a very low K232 value (0.093%) was recorded by Brahmi et al. (2020) for Algerian oils.

II. Fatty acid composition

The Fatty acid compositions of oils, expressed as percentage of total fatty acids, are summarized in Table 7. The following parameters saturated fatty acids (SFA), unsaturated fatty acids (UFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and PUFA/SFA ratios were also determined.

Table 07: Fatty acids composition of Hodna *P. lentiscus* seed oils.

Fatty acid (%)	HLHO	HLCO	<i>p</i> -value*
Lauric acid (C12:0)	0.253 ± 0.004	0.099 ± 0.000	0.0008***
Myristic acid (C14:0)	0.153 ± 0.000	0.075 ± 0.000	0.0000***
Palmitic acid (C16:0)	26.308 ± 0.030	18.331 ± 0.000	0.0000***
Palmitoleic acid (C16:1)	2.084 ± 0.000	0.900 ± 0.000	0.0000***
Margaric acid (C17:0)	0.065 ± 0.000	0.102 ± 0.000	0.0004***
Margaroleic acid (C17:1)	0.089 ± 0.001	0.116 ± 0.000	0.0014**

Stearic acid (C18:0)	2.043 ± 0.010	2.011 ± 0.000	0.0217*
Oleic acid (C18:1)	52.360 ± 0.074	57.945 ± 0.009	0.0001***
Linoleic acid (C18:2)	16.036 ± 0.030	19.579 ± 0.024	0.0000***
Linolenic acid (C18: 3)	0.106 ± 0.026	0.169 ± 0.000	0.0791
Arachidic acid (C20:0)	0.377 ± 0.00	0.520 ± 0.00	0.0001***
Eicosenoic acid (C20:1)	0.123 ± 0.06	0.148 ± 0.00	0.5891
ΣSFA	29.202 ± 0.02	21.140 ± 0.03	0.0000***
ΣMUFA	54.656 ± 0.02	59.110 ± 0.01	0.0000***
ΣPUFA	16.142 ± 0.03	19.749 ± 0.03	0.0001***
PUFA / SFA	0.552 ± 0.00	0.934 ± 0.00	0.0000***

SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids.

Each value represents the mean of two determinations ± SD.

Significance of differences (*t*-test, *P* < 0.05): **P* < 0.05, ***P* < 0.01, ****P* < 0.001

Twelve different fatty acids were identified and quantified in HLHO and HLCO oils. Six of them are saturated fatty acids (SFA) namely: lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), margaric acid (C17:0), stearic acid (C18:0), and arachidic acid (C20:0), four are monounsaturated fatty acids (MUFA): palmitoleic acid (C16:1), margaroleic acid (C17:1), oleic acid (C18:1) and eicosenoic acid (C20:1) and two polyunsaturated fatty acids (PUFA): linoleic acid (C18:2) and linolenic acid (C18:3).

The MUFA values obtained were between 59.110 ± 0.01% and 54.656 ± 0.02 %, and the PUFA values obtained were between 19.749 ± 0.03% and 16.142 ± 0.03% for HLCO and HLHO respectively, HLCO presents higher values than HLHO. It is worth mentioning that SFA were higher in HLHO (29.202%) than HLCO (21.140%). Overall, the content of UFA (MUFA + PUFA) was 70.80 ± 0.05% of total fatty acids for HLHO and 80.25 ± 0.04% for HLCO, making these oils, and particularly HLCO, highly unsaturated. Hence, the SFA: MUFA: PUFA balance for HLCO is roughly 1:3:1, matching the perfect blood lipoprotein lipid profile linked to a low risk of cardiovascular disease.

In both oils, oleic acid predominated as a fatty acid, presenting values between 57.945 % for HLCO and 52.36 % for HLHO. The HLCO presented somewhat higher values than HLHO. The only PUFA in the studied oils and the essential fatty acid, Linoleic acid, was the second most important fatty acid in HLCO ($19.579 \pm 0.024\%$) and the third in HLHO ($16.036 \pm 0.03\%$). The main SFA in the analyzed oils, palmitic acid, was the second most important fatty acid in HLHO ($26.308 \pm 0.03\%$) and the third in HLCO ($18.331 \pm 0.00\%$). It should be noted that the amount of oleic acid in both oils is three times higher than the amount of linoleic acid.

The majority of these results are within the range of findings reported by other researchers with different lentisk seed oils. The study of Djerrou (2014) for oil collected from Tamalous (Skikda) revealed the presence of oleic acid at 54.4%, palmitic acid at 22.5% and linoleic acid at 19.8%. Belyagoubi-Benhammou et al. (2018) obtained similar values for oleic acid (50.02 %), and linoleic acid (17.24 %), in the black fruit oil collected from Tlemcen. In the same way, oil collected from Izmir, Turkey showed a range between 54.45-56.45% for oleic acid, 25.05-27.79% for palmitic acid and 15.47% for linoleic acid (Akdemir et al., 2015). The results obtained from the Tunisian oil are between 42.09-55.66% for oleic acid, 22.22-29.26% for palmitic acid and 16.25-23.6% for linoleic acid (Mezni et al., 2014b). Furthermore, Chouaibi et al. (2013) found that oleic acid (50.39%) was the major acid, followed by palmitic acid (26.19%), and linoleic acid (18.74%). Our findings align also with findings of Chaabani et al. (2024) where the predominant fatty acids identified in n-hexane and 2-MeOx oil extracts were oleic acid (49.27–49.72%, respectively), linoleic acid (23.31–23.74%, respectively) and palmitic acid (22.15–22.41%, respectively). Monounsaturated fatty acids (MUFA) represented the majority of detected fatty acids, making up 50.83% to 51.11% of the total, followed by saturated fatty acids (SFA) at 25.09% to 25.19%, and lastly polyunsaturated fatty acids (PUFA) at 23.89% to 24.20%.

The same fatty acids were recorded by Ait Mohand et al. (2020) in the lentisk oils collected in Morocco where oleic acid represent 51.56-53.23%, linoleic acid 20.95- 23.77% and palmitic acid 20.51-23.01% . In Italy, according to Siano et al. (2020) *lentiscus* oils extracted over four successive years shows nearly the same results where oleic acid ranged between 44.20-44.88%, linoleic acid between 24.83-25.33% and palmitic acid between 22.42-23.01%.

Unsaturated fatty acids such as linoleic acid, are healthy fats that perform a variety of roles in cells. These roles include supplying lipids for cell membrane respiration and repair, as

well as having positive nutritional benefits and preventing cancer and coronary heart disease (Ait Mohand et al., 2020). However, MUFA-rich diets, including those high in oleic acid offer a number of advantageous benefits, including cholesterol decreasing (Chan et al., 1991), blood pressure reduction (Teres et al., 2008), anti-cancer (Carrillo Pérez et al., 2012) and prevent cardiovascular disease (Ait Mohand et al., 2020).

Hodna lentisk seed oils, particularly cold-extracted oil, are an excellent source of oleic acid due to their unique richness in the fatty acid. It should be noted that, out of all the *P. lentiscus* seed oils published in the literature, at least that which was consulted, HLCO has the highest oleic acid concentration (57.945%).

Despite the difference in the extraction process, it is interesting to note that the fatty acid profile for cold-extracted oil (HLCO) is broadly similar to that for (HLHO). It is noteworthy to note that the fatty acid profile of cold-extracted oil (HLCO) and hot-extracted oil (HLHO) is mostly identical, despite the differences in the extraction technique. Since UFA are more oxidative than SFA, the hot extraction actually causes a loss of UFA (Phan et al., 2019). As a result, using cold extraction on a larger scale to extract mastic seed oil will be appropriate, and consuming it will have significant health benefits.

III. Phenolic content and profile

III.1. Phenolic content

One of the most well-known classes of secondary metabolites present in plants are polyphenols, which are valued for their biological and pharmacological properties. Because phenolic compounds contribute to flavor and prevent fatty acids from oxidizing, their quantity is a crucial criterion for assessing the quality of edible oils (Belyagoubi-Benhammou et al., 2018). The phenolic contents of the two oils are presented in Figure 16. The amounts of these compounds differ significantly in the two oils and it reveals that the Hodna lentisk oils are rich in phenolic compounds.

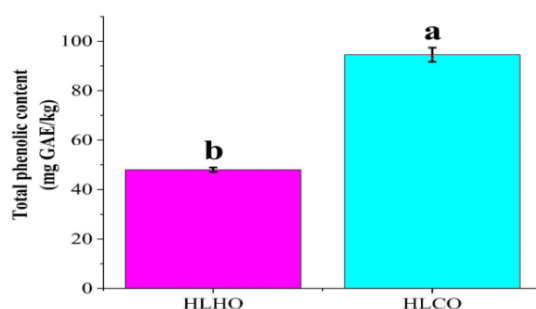


Figure 16: Total phenolic content of Hodna *P.lentiscus* oils, «a-b» indicates differences between oils

The total phenolic content of HLCO (94.14 ± 2.47 mg GAE/100g) was twice more than that of HLHO (48.02 ± 0.92 mg GAE/100g), which make HLCO a richer source of phenolic compounds. Because HLHO was extracted using a traditional approach that included adding water, it may have significantly larger water content than HLCO, which accounts for its lower total phenol concentration (Demnati et al., 2011). However, the value obtained for HLHO was higher than the findings of Brahmi et al. (2020), who obtained a value of 25.15 mg GAE/100 g oil for Algerian oil extracted with traditional method. The cold pressed oil HLCO shows high phenol content than the cold pressed oil from Guelma ($25.19 \mu\text{g GAE/mg}$) (Hamdi et al., 2023), and from Tunisia (20.41 mg GAE/100g) of Daoued et al. (2016) and low content than of Bouyahya et al. (2018) for Moroccan pressed oil where the total phenolic content was 22.61 mg GAE/g. Moreover, the cold-pressed oils produced in Cilento (Italy) by Siano et al. (2020) during four years of production (2015-2018) varies from year to year (435-616 mg GAE/kg) and are also lower than our results. Meanwhile Ben Ameur et al. (2024) recorded highest amount of phenolic compounds than our, with a phenolic content of 598.491 mg (GAE)/g for cold pressed oil harvested in Tunisia.

The higher total phenolic compound content in our oils, especially HLCO, contributes to enhanced resistance to oxidation (Meddeb et al., 2017), emphasizing that our lentisk's sub-arid origin and the cold extraction method provide better oil quality.

The literature has shown diversity in the phenolic compound content of lentisk oils. These variations are likely caused by a variety of variables, including genotypic factors, biotic circumstances (species, organ, and physiological stage), abiotic conditions (edaphic), soil type, and bioclimatic stages (Belyagoubi-Benhammou et al., 2018). Likewise, the growing

season, the stage of growth, and the technique of extraction might all be involved (Tahir et al., 2019).

Furthermore, as the literature indicates, numerous substances can react with the Folin-Ciocalteu reagent to produce a high apparent phenol content, meaning that the standard spectrophotometric determination of the polyphenols content with this reagent is not specific to polyphenols (Capannesi et al., 2000).

III.2. Phenolic profile

The polyphenolic compositions of Hodna sub-arid region lentisk oils are presented in Table 8 and the corresponding chromatograms are shown in Figure 17. A total of twelve phenolic compounds were identified, with nine and seven compounds in HLCO and HLHO, respectively.

Table 08: Phenolic profiles of Hodna *P. lentiscus* seed oils

Class	Compounds	HLHO (mg/100g oil)	HLHO (%)	HLCO (mg/100g oil)	HLCO (%)	<i>p</i> -value*
Phenolic acids	Gallic acid	0.34 ± 0.07	10.06	ND	ND	-
	Protocatechuic acid	ND	ND	ND	ND	-
	o-coumaric acid	ND	ND	ND	ND	-
	<i>p</i> -coumaric acid	0.09 ± 0.01	2.66	ND	ND	-
	Chlorogenic acid	ND	ND	0.06 ± 0.01	0.53	-
	Caffeic acid	ND	ND	0.13 ± 0.02	1.14	-
	Syringic acid	ND	ND	0.71 ± 0.03	6.3	-
	Ferulic acid	0.09 ± 0.01	2.66	0.15 ± 0.01	1.321	0.014
	Sinapic acid	0.95 ± 0.02	28.11	ND	ND	-
Flavanols	Catechin	ND	ND	7.99 ± 2.25	70.34	-
Flavones	Luteolin	0.51 ± 0.01	15.10	0.65 ± 0.02	5.3	0.006

	Apigenin	0.13 ± 0.03	3.85	0.12 ± 0.01	1.1	1.00
Flavonols	Myricetin	ND	ND	0.12 ± 0.01	1.1	-
	Quercetin	1.27 ± 0.05	37.57	1.43 ± 0.30	12.6	0.115

Each value represents the mean of two determinations $\pm$ SD.

Significance of differences (*t*-test, $P < 0.05$): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, ND: not detected.

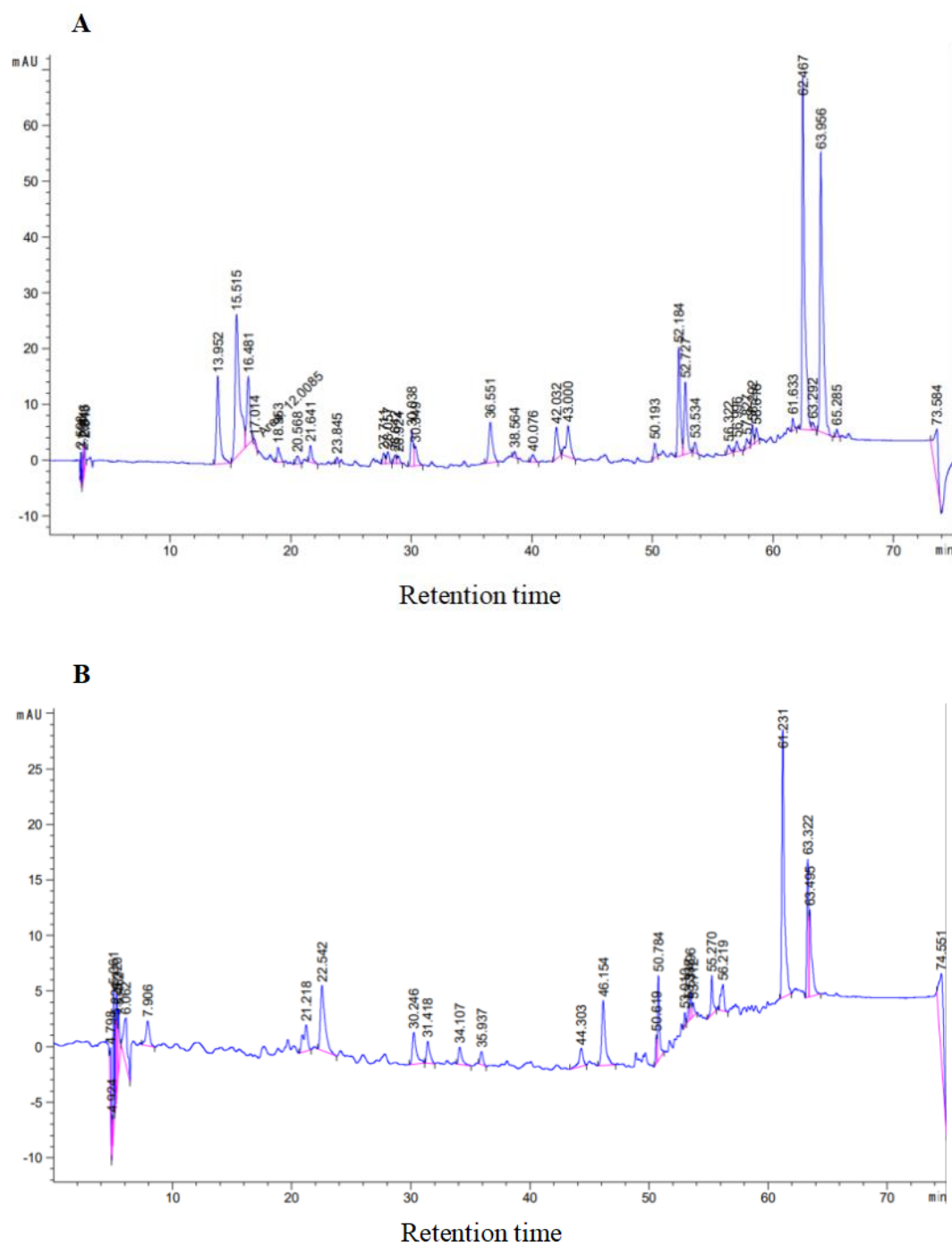


Figure 17: (A) chromatogram of phenolic profile of HLCO, (B) chromatogram of phenolic profile of HLHO.

Different oil extraction processes led to differences in polyphenolic compositions of the oils. In addition to ferulic acid (0.09-0.15 mg/100g), luteolin (0.51-0.65 mg/100g), quercetin (1.27-1.43 mg/100g), and apigenin (0.13-0.12 mg/100g), which were quantified in both oils, gallic acid, catechin, caffeic acid, syringic acid, *p*-coumaric acid, sinapic acid, myricetin, and chlorogenic acid were found in only one of the oils. Four groups of phenolic compounds were identified in the HLCO: five phenolic acids (10.61%), one flavanol (70.33%), two flavonols (13.7%), two flavones (6.4%). Overall, total flavonoids (flavanol, flavonols and flavones) constitute more than 90% of the phenolics detected in HLCO. On the other hand, three groups of phenolic compounds were identified in the HLHO: four phenolic acids (43.49%), two flavone (18.95%) and one flavonol (37.57%). In total, total flavonoids (flavonol and flavone) represented 56.52% of the polyphenolics identified in HLHO. Our findings suggest that HLCO is more diversified in terms of phenolic compounds. The most predominant phenolic compounds of HLCO were catechin (flavanol) and quercetin (flavonol), which accounted for 70.33% and 12.6% of all detected compounds, respectively. Catechin has diverse activities, including being antioxidant, antimicrobial, anti-inflammatory, anti-diabetes, anti-obesity, anti-cancer, chemopreventive and cardioprotective (Ye and Augustin, 2019). Similarly, quercetin is a flavonoid well-known for its exceptional antioxidant, anti-cancer, anti-inflammatory, antimicrobial, anti-allergic, anti-asthmatic, anti-hypertensive, anti-diabetes, anti-obesity properties, as well as its ability to reduce blood pressure and serum cholesterol levels (Aghababaei and Hadidi, 2023). The other phenolic compounds identified in HLCO were syringic acid (0.71 mg/100g), luteolin (0.65 mg/100g), ferulic acid (0.15 mg/100g), caffeic acid (0.13 mg/100g), apigenin (0.12 mg/100g), myricetin (0.12 mg/100g), chlorogenic acid (0.06 mg/100g). Our findings indicated that flavonoid-type phenolics could be the primary contributor to the nutritional and sensory properties of HLCO, as well as its resistance to autoxidation and photooxidation. Regarding HLHO, quercetin (1.27 mg/100g) was the dominant phenolic, accounting for 37.57% of all polyphenolic compounds. Sinapic acid (0.95 mg/100g) was the second most abundant compound, comprising 28.11% of all quantified polyphenols. Sinapic acid, which is a phenolic acid commonly found in oilseeds, berries, spices, rice, oat, wheat, rye, citrus fruits, Brassica-group vegetables (radish, cabbage, broccoli, and turnips), and vinegar, has been linked to numerous therapeutic properties, such as antioxidant, antimicrobial, anti-inflammatory, anti-cancer, anti-hyperglycemic, anti-diabetic, anti-hypertensive, hepatoprotective, renoprotective, and neuroprotective (Pandi and Kalappan,

2021). Other phenolics found in HLHO included luteolin (0.51 mg/100g), ferulic acid (0.09 mg/100g), gallic acid (0.34 mg/100g), *p*-coumaric acid (0.09 mg/100g). Overall, polyphenolics found in both oils are flavonoids and phenolic acids. In contrast to our findings, the presence of protocatechuic acid was previously reported in cold-pressed Algerian (0.03 mg/100g) and Tunisian (0.62 mg/100g) *P. lentiscus* seed oils (Brahmi et al., 2020, Daoued et al., 2016). On the other hand, our results were partially confirmed by Daoued et al. (2016), who estimated comparatively high amounts of caffeic (9.71 mg/100g), *p*-coumaric (2.98 mg/100g), ferulic (5.46 mg/100g), syringic (4.18 mg/100g), and gallic acid (0.84 mg/100g) along with *p*-hydroxybenzoic (7.58 mg/100g) in the cold-pressed seed oil produced in Tunisia. In addition to these, the occurrence of tyrosol, 4-hydroxyphenylacetic acid, vanillic acid, trans-4-hydroxy-3-methoxycinnamic acid, oleuropein aglycone, kaempferol, salicylic acid, naphtoresorcinol, apigenin, coumarin, carnosic acid, and trans-cinnamic acid was reported in the oils pressed from *P. lentiscus* seeds grown in different locations of Tunisia (Mezni et al., 2018). Siano et al. (2020) also reported rutin, myricetin, eryodictiol, naringenin, quercetin-3-O-glycoside and diosmetin in cold-pressed Italian seed oils. Unlike previous studies, we also detected catechin, sinapic acid, and chlorogenic acid in *P. lentiscus* seed oil for the first time. *P. lentiscus* seed oils are excellent sources of various polyphenolics with promising therapeutic effects. Furthermore, these biologically active compounds influence the nutritional value, sensory appeal, and storage stability of the products (Siger et al., 2008).

IV- Tocols profile

The tocols composition of Hodna lentisk oils is listed in Table 9. A total of eight individual tocols compounds, including all forms of tocopherols and tocotrienols, were identified, as seven for each of the oils.

Table 09: Tocopherols and tocotrienols composition of Hodna *P. lentiscus* seed oils.

Compounds	HLHO			HLCO			*p-value
	mg/Kg	Tocotrienols (%)	Tocols (%)	mg/Kg	Tocotrienols (%)	Tocols (%)	
α -tocotrienol	3.67 $\pm$ 0.70	19.36	4.3126	ND	ND	ND	-
β -tocotrienol	8.11 $\pm$ 0.01	42.70	9.53	7.44 $\pm$ 0.22	29.18	10.90	0.233
γ -tocotrienol	3.72 $\pm$ 0.24	19.58	4.37	8.02 $\pm$ 0.17	31.45	11.75	0.005 **
δ -tocotrienol	3.49 $\pm$ 0.10	18.37	4.10	10.04 $\pm$ 0.47	39.37	14.71	0.138
Total tocotrienols	18.97 $\pm$ 0.71	100	22.32	25.5 $\pm$ 0.59	100	37.35	-
	Tocopherols (%)			Tocopherols (%)			
	mg/Kg	Tocopherols (%)	Tocols (%)	mg/Kg	Tocopherols (%)	Tocols (%)	
α -tocopherol	59.96 $\pm$ 1.08	90.70	70.46	8.49 $\pm$ 0.74	19.85	12.43	0.001 **
β -tocopherol	0.14 $\pm$ 0.01	0.21	0.17	9.00 $\pm$ 0.57	21.04	13.18	0.004**
γ -tocopherol	6.01 $\pm$ 0.53	9.09	7.06	19.64 $\pm$ 0.69	45.92	28.77	0.004**
δ -tocopherol	ND	ND	ND	5.64 $\pm$ 0.90	13.19	8.26	-
Total tocopherols	66.10 $\pm$ 0.77	100	77.69	42.85 $\pm$ 1.68	100	62.65	-

Each value represents the mean of two determinations $\pm$ SD.

Significance of differences (*t*-test, $P < 0.05$): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, ND: not detected.

Tocopherols and tocotrienols together referred to as "tocols" and summed up as "vitamin E," are a class of eight chromanol homologues with antioxydant activity (Delgado et al., 2020). These naturally occurring monophenolic compounds are found in plant tissues and consist of a chromanol ring and a hydrophobic side chain (phytyl in tocopherols, isoprenyl in tocotrienols). The methyl substituents on the phenolic part of the chromanol ring vary among

the individual tocopherols (α -, β -, γ -, and δ -tocopherols) and their corresponding tocotrienols (tocotrienols).

The oil samples showed a different chromatographic profile, recording qualitative and quantitative tocol variations between the two extraction processes. The total tocols content varied from 68.35 ± 2.27 for HLCO to 85.08 ± 1.48 mgkg⁻¹ of oil for HLHO. It was clear that hot-pressed oil was significantly richer in tocols than cold-pressed oil. Similarly, HLHO contained more tocopherols (66.10 ± 0.77 mg kg⁻¹) than HLCO (42.85 ± 1.68 mg kg⁻¹). Tocopherols dominated in the two oils, representing over 62.70% for HLCO and 77.7% of the total tocols content for HLHO. The tocotrienol content of HLCO (25.5 ± 0.59 mg kg⁻¹) was higher than that of HLHO, equivalent to 37.30% of all tocols detected. It is worth mentioning that tocotrienol levels in foods are generally low compared with those of tocopherols, but do not affect the assessment of vitamin E dietary intake (Cerretani et al., 2010).

As it is mentioned in Table 10, three tocopherol forms were determined in HLHO: α -tocopherol (59.96 ± 1.08 mg kg⁻¹), β -tocopherol (0.14 ± 0.01 mg kg⁻¹) and γ -tocopherol (6.01 ± 0.53 mg kg⁻¹) corresponding to an average of 90.7, 0.21 and 9.09% respectively. Evidently, α -tocopherol was the most abundant tocopherol and the major compound in all HLHO tocols, accounting for 70.45% of total tocols. The β -tocopherol was in a tiny amount (0.16%) and δ -tocopherol was not detected. Theoretically, Out of all the homologs, α -tocopherol has the strongest biological action. However, the other forms of tocopherol also have high vitamin E activity and antioxidants properties (Traber and Atkinson, 2007, Uluata and Özdemir, 2012). On the other side, all tocotrienol forms were identified in the HLHO: α -tocotrienol (3.67 ± 0.70 mg kg⁻¹), β -tocotrienol (8.11 ± 0.33 mg kg⁻¹) γ -tocotrienol (3.72 ± 0.24 mg kg⁻¹) and δ -tocotrienol (3.49 ± 0.10 mg kg⁻¹) corresponding to an average of 19.36, 42.71, 19.59 and 18.38% respectively. β -tocotrienol was The most abundant tocotrienol (42.71%) and the other forms are found in small and almost similar proportions.

The chromatographic analysis of HLCO tocols showed that all four forms of tocopherols were detected and ranged from 5.64 ± 0.90 to 19.64 ± 0.69 mg kg⁻¹, of which an average of 19.85% corresponds to α -tocopherol, 21.04% to β -tocopherol, 45.92% to γ -tocopherol and 13.18% to δ -tocopherol. γ -tocopherol was the most abundant of tocol forms, representing 70.45% of total tocols. In contrast, only three tocotrienol forms were identified in the HLCO: β -tocotrienol (7.44 ± 0.22 mg kg⁻¹) γ -tocotrienol (8.02 ± 0.17 mg kg⁻¹) and δ -tocotrienol (10.04 ± 0.47 mg kg⁻¹) corresponding to an average of 29.18, 31.45 and 39.37% respectively. Despite containing only three forms of tocotrienols, this oil was richer in tocotrienols than

HLHO and δ -tocotrienol was the most abundant. The other two forms are found in almost equivalent quantities and δ -tocopherol was not detected.

As reported in the literature, the study conducted in Algeria by Charef (2011) partially characterized the tocols of *P. lentiscus* oil collected in Tipaza. The values of α -tocopherol recorded respectively for black and red seeds between 135.0 and 355.0 mg/kg of oil, β -tocopherol and γ -tocopherol values between 16.0 and 157.0 mg/kg of oil and δ -tocopherol values between 1.4 and 73.0 mg/kg of oil. The values of the four tocopherols determined for black seeds are higher than our results. The tocopherols content of oil samples harvested in five locations in Algeria (Collo, Blida, Khemis Miliana, Berrouaghia and Djelfa) ranged from 93.06 to 546.56 mg/100 g of lipids (Bakhti et al., 2024).

On the contrary, several studies on the tocols of Tunisian lentisk oils have been documented. The major tocopherols found by Mezni et al. (2020) where α -tocopherol and γ -tocopherol accounting for 119 mg/kg and 23 mg/kg, respectively, which is high than our finding. Our results align with those obtained by Dhifi et al. (2013) who showed that α -tocopherol presented 93.62% of total tocopherols and that δ -tocopherol was not detected. Similarly, Ghzaïel et al. (2021) recorded a value of α -tocopherol (68.10 mg/kg) close to our finding. The content of tocols in the *P. lentiscus* oil harvested from eight locations of the north and center of Tunisia (Mezni et al., 2014a) varied between 62.43 and 118.16 mg/kg. The α -tocopherols (44.76-96.77 mg/kg) were found in important quantities compared to γ -tocopherol (14.56-22.12 mg/kg). High total tocols content than our finding was found by Daoued et al. (2016) where it was 181.86 mg/100 g oil, where major tocols were γ -tocopherol (111.07 mg/100 g), α -tocopherol (38.37 mg/100 g oil) and δ -tocotrienol (16.12 mg/100 g oil). Very high tocopherol contents were also recorded by Ben Ameur et al. (2024) where α -tocopherol was 957.88 mg/Kg. Therefore, compared to the aforementioned data, the tocols contents found in this Tunisian oil are very remarkable.

Tocopherol profile of *Pistacia lentiscus* oils collected from Tabarka region in North of Tunisia extracted using two solvents: 2-methyloxolane and n-hexane by means of soxhlet extractor showed that α -tocopherol constituted the majority of the tocopherols, accounting for over 90% of the total, whereas the combined amount of β and γ -tocopherol is only around 9%. δ -tocopherol is not present in the extracts of 2-MeOx or n-hexane (Chaabani et al., 2024).

The literature suggests that a number of factors, including origin, extraction method, growth circumstances (weather, growing season, sun intensity, and soil), ripening stage, and

type of oil seed, might be responsible for the discrepancy between the results found for tocols in this study and those reported (Szydłowska-Czerniak et al., 2008, Neđeral et al., 2012).

Lastly, it should be noted that while being stored, the protocol content is partially destroyed. Additionally the decomposition can occur due to the influence of light and temperature, which are highly significant factors in addition to the oxygen effect (Bauernfeind and Desai, 1977, Ayyildiz et al., 2015).

V. Trolox equivalent antioxidant capacity

The DPPH assay is a commonly used method to assess a compound's capability to behave as a hydrogen donor or free radical scavenger as well as to evaluate the overall antioxidant capacity of food (Prakash, 2001). This method has been successfully used to study antioxidant properties in different chemical and biological mixtures, including edible oils (Parry et al., 2005).

DPPH radical scavenging activities, were tested, the results are depicted in Figure 18. A very high free radical scavenging activity was recorded for both oils, but that of HLHO (113.81 mM Trolox in 100 g) was slightly higher than that of HLCO (107.47 mM Trolox in 100 g). There was no significant difference on the DPPH radical scavenging activity according to the extracting process.

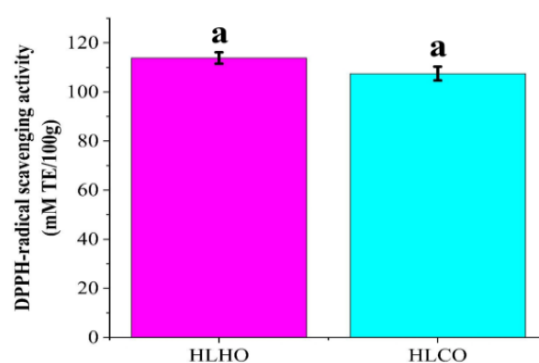


Figure 18: DPPH-radical scavenging activity of Hodna *P. lentiscus* oils, «a and b» indicates differences between oils

In our study, we compared our results with studies using units similar to ours, which are rare. Daoued et al. (2016) highlighted that seed oils expressed strong DPPH and ABTS radical scavenging activity and pancreatic lipase inhibitory activity *in vitro*. Mezni et al. (2014b), recorded (80 µg of Trolox/g oil) from lentisk oils of overripe pulp, (28 µg of Trolox/g oil) for

whole unripe fruit and (0.9 μg of Trolox/g oil) for unripe seed oil, these DPPH capacity values are much lower than our results. A range of 0.322–0.457mmol Trolox/mL oil was obtained for oils from different regions of Tunisia (Gaout, 2012). These values are also much lower than ours.

The antioxidant action of seed oils is attributed to their phytochemical composition, which includes carotenoids, phenolic compounds, tocopherols, and chlorophyll. The two major antioxidants present in oils are tocopherols and phenolics (Belyagoubi-Benhammou et al., 2018). In this study, HLCO was twice as rich in polyphenols as HLHO, over of 90 % of which are flavonoids, catechin being the major compound followed by quercetin. On the other hand, HLHO was formed mainly of phenolic acids and flavonoids, quercetin and sinapic acid being the two main components. It's important to note that although both oils have different phenolic compositions, they presented the same scavenging power. Due to the presence of inherent powerful antioxidants, lentisk oils exhibited a significant *in vitro* antioxidant activity. This activity in HLHO is probably due to its phenolic acids and flavonoid content, especially quercetin and sinapic acid. Similarly for HLCO it may be due to its high content of flavonoids such as catechin and quercetin. Veiko et al. (2021) reported that quercetin was a more potent antioxidant than favan-3-ol (+)-catechin and flavanon naringenin. Furthermore, quercetin showed a much higher apparent reaction rate constant and lower activation energy for DPPH reduction than catechin, and naringenin did not react with the DPPH radical. Moreover, previous reports showed that the isolated component quercetin has demonstrated improved antioxidant activity (Sambandam et al., 2016). Quercetin and some of its derivatives were found to be effective scavengers of the free radicals produced by DPPH (Dok-Go et al., 2003). According to a recent study, quercetin is an effective antioxidant and anti-inflammatory, and the quantity of phenolic hydroxyl groups in a sample strongly correlates with its antioxidant activity (Tian et al., 2021).

Sinapic acid also has an effective scavenging capacity that could be a powerful oxidant scavenger (Zou et al., 2002). More recently, Yang et al. (2021) proposed that methoxyl might increase the antioxidant activity in the DPPH system by showing that the sinapic acid group's antioxidant activity was higher than the ferrulic acid group's. Moreover, the extracts rich in sinapic acid derivatives have shown significant radical neutralising activity, while sinapic acid has a higher radical neutralising activity than sinapine (Thiyam et al., 2006). The antioxidant impact of twenty binary combinations (synergy, additivity or antagonism) of four phenolic acids (coumaric acid, gallic acid, caffeic acid and chlorogenic acid) and four flavonoids

(quercetin, catechin, rutin and epicatechin) was assessed *in vitro* using the DPPH assay. The results showed that the combination of phenolic acids and flavonoids can have an antagonistic or additive impact on DPPH inhibition, while the binary flavonoid-flavonoid combination can only have a synergistic effect. Chlorogenic acid presented the highest inhibition of DPPH, whereas coumaric acid did not present any DPPH inhibition (Mercado Mercado et al., 2020).

Tocols are known for their antioxidant activity, and it is believed that all their biological activities derive from their capacity to protect lipids from oxidation (Shahidi and De Camargo, 2016). HLHO was richer in tocols than HLCO; α -tocopherol was the major compound. On the other hand, γ tocopherol was the most abundant tocols in HLCO. These results showed that both oils can be considered excellent source of vitamin E. The antioxidant activity of these oils and more particularly HLHO may also be due to their high tocopherol content such as α -tocopherol and γ tocopherol, as they are known for their effective radical scavengers and defending the body against free radical attack by protecting MUFA and PUFA from oxidation (Delgado et al., 2020). It was demonstrated that γ - and δ -tocopherols affected the first phase of the DPPH elimination reaction, while α -tocopherol affected the second (Broznić et al., 2016). Furthermore, the antioxidant activity of tocopherols can be expressed as $\delta > \gamma > \beta > \alpha$ (Wanasundara and Shahidi, 2005). Generally, α -tocopherol has better antioxidant activity than γ -tocopherol in fats and oils (Seppanen et al., 2010).

α -tocopherol is part of an antioxidant network that includes other antioxidant compounds, which appears to make it the principal and most efficient antioxidant *in vivo* for breaking lipid-soluble chains. Noteworthy is the fact that α -tocopherol and polyphenolic compounds can work synergistically *in vivo* (Murakami et al., 2003).

The antioxidant power of mastic oils may be attributed to substances other than phenolics. According to several studies the strong antioxidant activity of vegetable oils has been linked to phospholipids, including phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine (Segwa et al., 1995). According to some writers, linoleic acid and other specific fatty acids are crucial for the antioxidant properties of oils (Ramaprasad et al., 2006). Finally, the presence of all these classes of compounds in *P. lentiscus* seed oil may explain this high antioxidant activity.

VI. Antimicrobial activity

Eleven microbial species were analyzed to assess the antimicrobial activity. The five pathogenic bacteria, three Gram positive, were *Staphylococcus aureus*, *Listeria monocytogenes* and *Bacillus cereus* and two Gram negative *Pseudomonas aeruginosa* and *Escherichia coli*. The six fungi, including one yeast, were *Fusarium culmorum*, *Umbelopsis ramanniana*, *Aspergillus carbonarius*, *Aspergillus flavus* and *Aspergillus parasiticus* and *Candida albicans*.

The data of our study leads to the conclusion that both oils studied had no antibacterial action against the strains tested. This finding is in line with several other studies on mastic oil, even if the findings have varied across them.

Our results are in agreement with those of Azizi et al. (2022) who revealed that *P. lentiscus* oil of El Taref, Skikda and Guelma had no inhibitory effect against *B. klebsiella* and *S. aureus* while it was effective against *Verticillium sp.*, *Phytophthora sp.* and *Pythium sp.* Beldi et al. (2020) demonstrated that oils harvested from different regions in the east of Algeria have no antibacterial activity against *P. aeruginosa*, *K. a pneumonia* and *S. aureus* while these oils exhibited an inhibitory effect against (*Verticillium sp.*, *Phytophthora sp.* and *Pythium sp.*).

Moreover, no antimicrobial effect from Algerian lentisk oil was recorded towards *E. coli* and *P. aeruginosa* and against *A. niger*, *A. flavus*, *A. ochraceus*, *M. rammaniarrus*, *A. parasitus* and *C. albicans*. However, this oil exhibited only a small zone of inhibition (diameter: 1 mm) against Methicillin-resistant *S. aureus* strains (Brahmi et al., 2020).

Mastic fixed oils from Tunisia extracted by traditional and pressing process showed no inhibitory effect towards *E. coli* and *S. typhimurium* (Mezni et al., 2012). Similarly, Mezni et al. (2015) reported that no antibacterial and antifungal effects, assessed towards *L. monocytogenes*, *E. coli*, *P. areogenusa*, *B. subtilis*, *S. typhimurium* and *S. Arizona* and against *A. flavus* and *C. albicans*, were found.

Furthermore lentisk oil from Tabarka (Northeast of Tunisia) extracted with Soxhlet apparatus showed no inhibitory effect against these strains: *Enterococcus faecalis* (ATCC 29212), *Methicillin-resistant Staphylococcus aureus* (MRSA, ATCC 6538), *Pseudomonas aeruginosa* (ATCC 2134), *Escherichia coli* (ATCC 35218), *Listeria monocytogenes* (ATCC

19195), *Salmonella enteritidis* hospital strain (DMB 560), *Candida albicans* (ATCC 1024), *Fusarium solani* and *Rhizoctonia solani* (RS5.2) (Abidi et al., 2023).

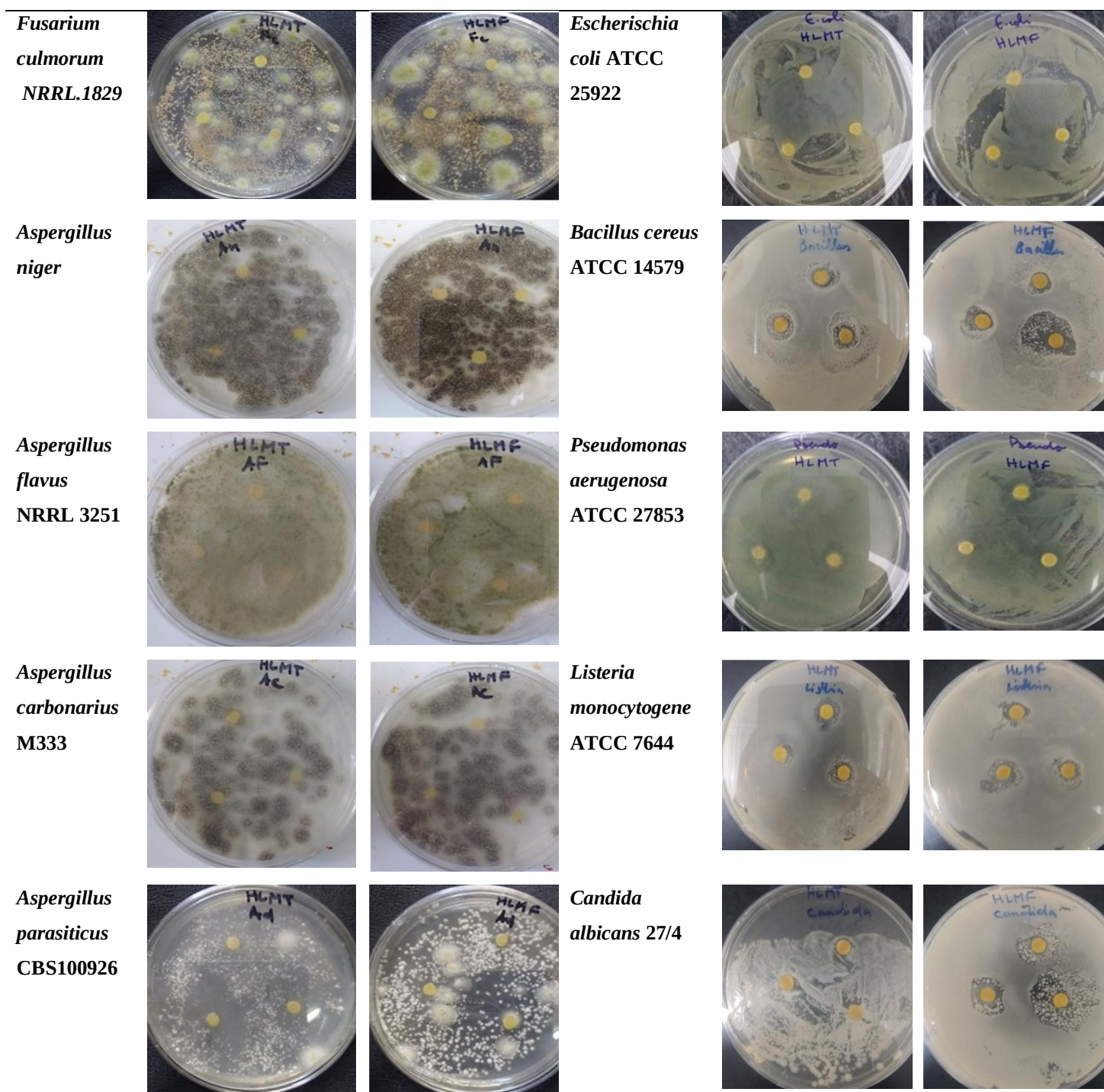
On the contrary Dhieb et al. (2021), found that lentisk oil from Bizerte in north of Tunisia have antimicrobial effects against all of the tested bacteria (*L. innocua*, *S. enterica*, *S. flexneri* and *E. faecalis*) and towards the most medically important and emerging species of *Candida* (*C. tropicalis*, *C. parapsilosis* and *C. glabrata*). These authors affirm that this activity varies depending on the microorganism tested.

Even though the richness of our oils in polyphenols, particularly flavonoids, no inhibitory effect was recorded against the microbial strains tested, although these compounds are known for their antimicrobial power (Nguyen and Bhattacharya, 2022, Gopal et al., 2016, Przybylska Balcerek et al., 2022). Various other secondary metabolites also have potential antimicrobial properties (Mabona et al., 2013).

The results might be impacted by the technique employed to evaluate antibacterial activity (Boyanova et al., 2005). Because diverse, non-standard procedures are used for inoculum preparation techniques, inoculum size, incubation conditions, growth medium, and end-point determination, it is frequently difficult to compare the results of antimicrobial studies. The standard technique for conducting regular antimicrobial susceptibility testing in many clinical microbiology laboratories is the agar disc diffusion test (CLSI, 2015). The strains that were examined were likely not sensitive probably because the antimicrobial agents in the oil could not disperse uniformly throughout the agar.

Table 10: Antimicrobial results.

Fungal strains	HLHO	HLCO	Bacterial strains	HLHO	HLCO
<i>Umbelopsis ramanniana</i> NRRL 1829			<i>Staphylococcus aureus</i> ATCC 25923		



VII. Wound healing activity

The development of novel wound healing agents is one of the emerging disciplines in current biomedical sciences and numerous studies have been carried out utilizing different wound healing models. The healing potential of lentiscus oil was evaluated on rats by induction of a skin wound by circular excision. The effectiveness of wound healing was

determined by a variety of qualitative and quantitative parameters, including macroscopic observation, contraction rate calculation, and histological examination.

VII.1. Irritation test

Figure 19 displays the outcomes of our oils' acute dermal toxicity test after 24 hours. Determining acute toxicity is the first of the toxicological studies to be undertaken for a substance with supposed pharmacological properties. The main effects sought in this type of study are clinical signs, apparent pathological changes and mortality. In this irritation test, animals were frequently observed after topical application of HLCO and HLHO during the fourteen days of the test. No mortality or signs of toxicity were observed. In addition, there were no signs of inflammation, skin irritation, erythema, eschar, edema or other reactions on the skin of the animals. Based on our data, short-term treatment with HLCO and HLHO appears safe. On the other hand; Djerrou et al. (2013) showed that *P. lentiscus* oil was slightly irritating after a single application to rabbits and that irritant reactions accumulated after multiple applications over a period of 28 days.

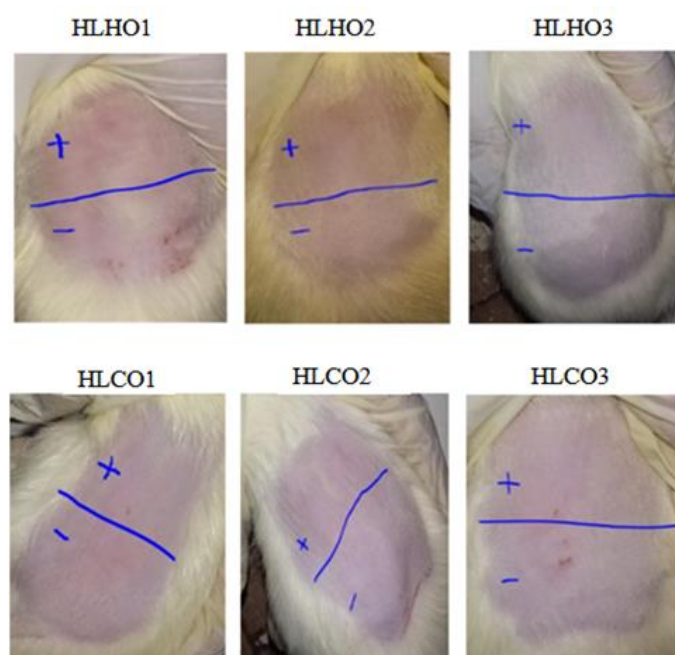


Figure 19: Irritation test after 24 hours.

VII.2. Weight evolution during healing treatment

The rats were weighed before and during treatment to assess the effect of the experimental treatments on body weight. Figure 20 shows that throughout the 18 days of

treatment, the development of the rats in all groups tested was normal and unaffected by the injuries.

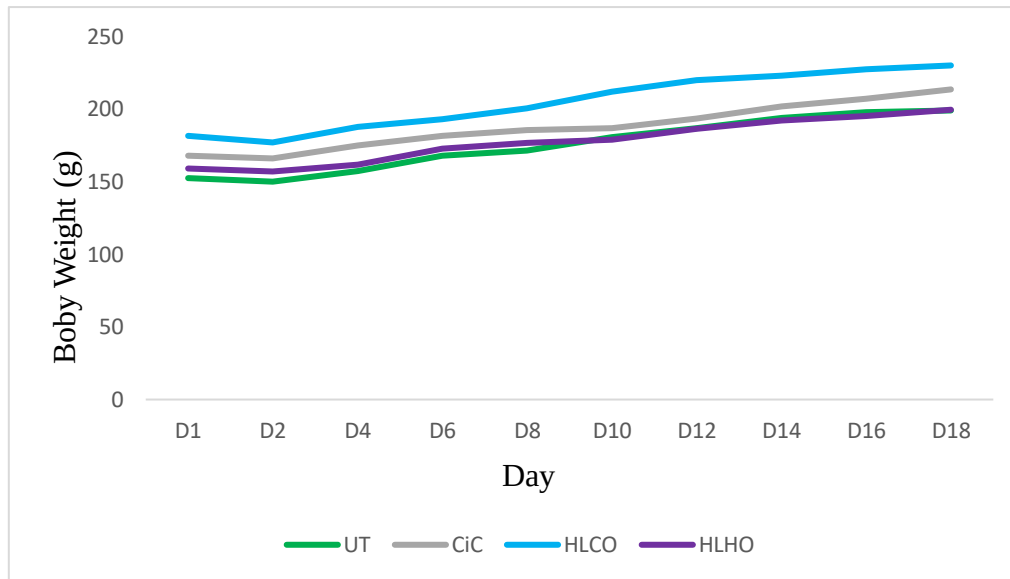


Figure 20: Evolution of the body weight of untreated (UT) and treated rats (CIC, HLHO and HLCO) over the 18 days of the experiment

VII.3. Macroscopic evaluation of wound healing

The wounds were regularly measured every 3 days during the healing study. Figure 21 shows the macroscopic evolution of wounds during the healing treatment.

A steadily developing blackish-red crust was visible during the first week following the incision; by day 5, the crust had fully set in and granular tissue, mostly made up of collagen-synthesizing fibroblasts and myofibroblasts, was beginning to form. This reveals the formation of blood clots with cellular debris, indicating the start of the healing process. As a result, during macroscopic examination, every incision was discovered to be rather clean and free of inflammatory signs such as swelling and redness. From day 7 to day 11, the experiment showed a fall in crust along with the onset of epidermal tissue formation. The HLCO group's crust was removed on day 7, the CIC and HLHO groups' crusts fell on day 8, and the UT group's crust continued to form until day 11. In both groups, we observed that wounds healed quickly once the crusts collapsed, especially starting on day 12. In wounds treated with HLCO, HLHO and CIC, nearly full closure was seen on day 18, indicating re-epithelialization and tissue healing. At the conclusion of the trial, the UT group still had an open wound.

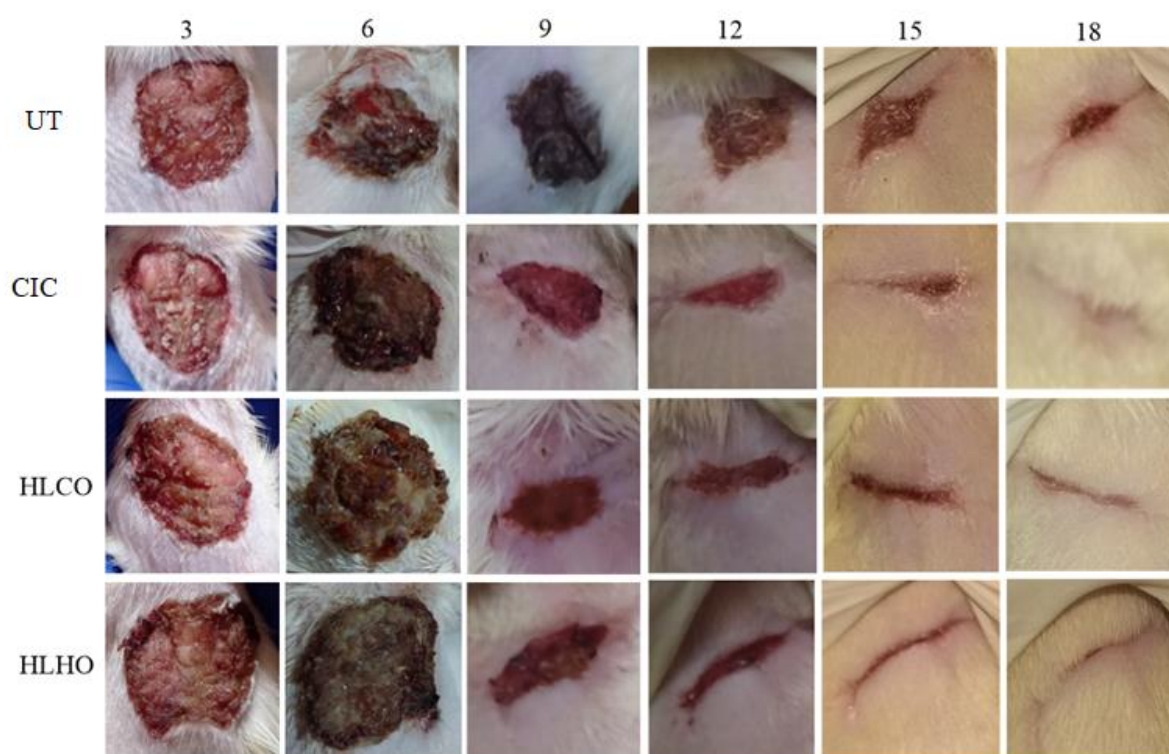


Figure 21: Macroscopic images of skin wound healing for different groups in day 3, 6, 9, 12, 15 and 18. UT: Untreated group, CIC: Cicatryl-treated group, HLCO: Hodna lentisk cold oil treated group, HLHO: Hodna hot lentisk oil treated group.

VII.4. Evolution of wound contraction rates

As mentioned above, the wound excision areas of treated and untreated animals in the different groups were regularly measured every three days. The wound contraction percentages were calculated and compared. Table 11 shows the evolution of wound contraction percentage results over time. All treated animals showed a significant reduction in wound area ($P < 0.05$). At day 3, we observed a slight reduction in the wound area with varying percentages in all the groups. It is interesting to note that the treated groups showed an enhanced pattern of healing in 9-12 days, with percentages of wound contraction of 50 %, 56.33%, and 60.25%, for HLHO, HLCO, CIC groups, respectively, except the UT group (17.21%). The percentage of contraction at day 15 was the greatest in the CIC group (78.20%), followed immediately by the HLCO group (75.71%), whereas the percentage for the UT group was the lowest (38.91%). In addition, HLCO group showed comparable wound contraction efficacy to the reference drug group CIC during the healing period, particularly from day 9 to day 18.

By the end of the experiment (day 18), CIC showed the highest percentage of wound contraction with 87.05 %, a value very close to that obtained with HLCO and HLHO (86.95 % and 86.25 % respectively). However, the UT group had the lowest wound contraction rate with a value of 43.93%. Our study indicates that the administration of HLHO and HLCO oils promotes the wound contraction especially the cold pressed oil HLCO which was nearly similar to the standard treatment CIC during almost all healing periods.

Table 11: Effect of different treatments on the evolution of the healing process of excision wounds

Groups	Wound contraction (%)					
	Days					
	3	6	9	12	15	18
UT	1.85 ± 0.06	9.8 ± 3.6	17.21 ± 3.37	32.07 ± 3.80	38.91 ± 2.21	43.93 ± 1.63
CIC	2.82 ± 0.96	10.25 ± 2.93	60.25 ± 4.00	68.58 ± 4.44	78.20 ± 4.00	87.05 ± 0.58
HLCO	6.20 ± 1.81	16.10 ± 4.69	56.33 ± 4.08	64.37 ± 5.28	75.71 ± 5.82	86.95 ± 0.46
HLHO	2.41 ± 0.78	15.54 ± 2.38	50 ± 2.57	58.08 ± 4.20	70.74 ± 4.70	86.25 ± 4.41
<i>p-value*</i>	0.005**	0.037*	<0.001***	<0.001***	<0.001***	<0.001***

Values are expressed as mean ± SD (n=5); * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ when treated groups are compared to the UT group

VII.5. Histopathological analysis of wounds

Figure 22 illustrates the results of the histopathological study of wound sections on day 18 of the experiment. Histological sections from the UT group showed an inflamed dermis, infiltrated epidermis and incomplete epithelium with poorly formed granulation tissue, fewer collagen fibers, the presence of numerous inflammatory cells and thinning of the mucosal body, indicating incomplete wound healing.

In the HLHO and HLCO groups, the histological analyses revealed improved scarring and nearly total re-epithelialization and restructuring of the dermis: return *ad integrum*, dermal scar fibrosis, and no sign of appendages. In the CIC group, there was a fibro-collagen dermis and rarefaction of the pilosebaceous appendages. The outward healing of the three treated groups was remarkable, especially as they showed no depressions, a high epidermal thickness corresponding to hyperplasia and low inflammation. These are all elements that

attest to tissue repair phenomena. Out of all the groups, the CIC group heals the fastest. The results of the histological analysis accord with the wound contraction rate and the outcomes of the macroscopic assessment.

This study is the first to evaluate the *in vivo* wound-healing properties of *P. lentiscus* oils extracted from the Hodna region and to compare the wound-healing properties of the hot and cold extracted oils. Based on wound contraction percentages, histological examination, and macroscopic examination of the healing process, HLCO cold-extracted mastic oil has a faster and slightly better healing profile than HLHO hot-extracted oil. This suggests that, as with CIC, topical application of the two Hodna lentisk subarid oils, particularly the cold-extracted HLCO, to the wound could significantly improve wound healing process.

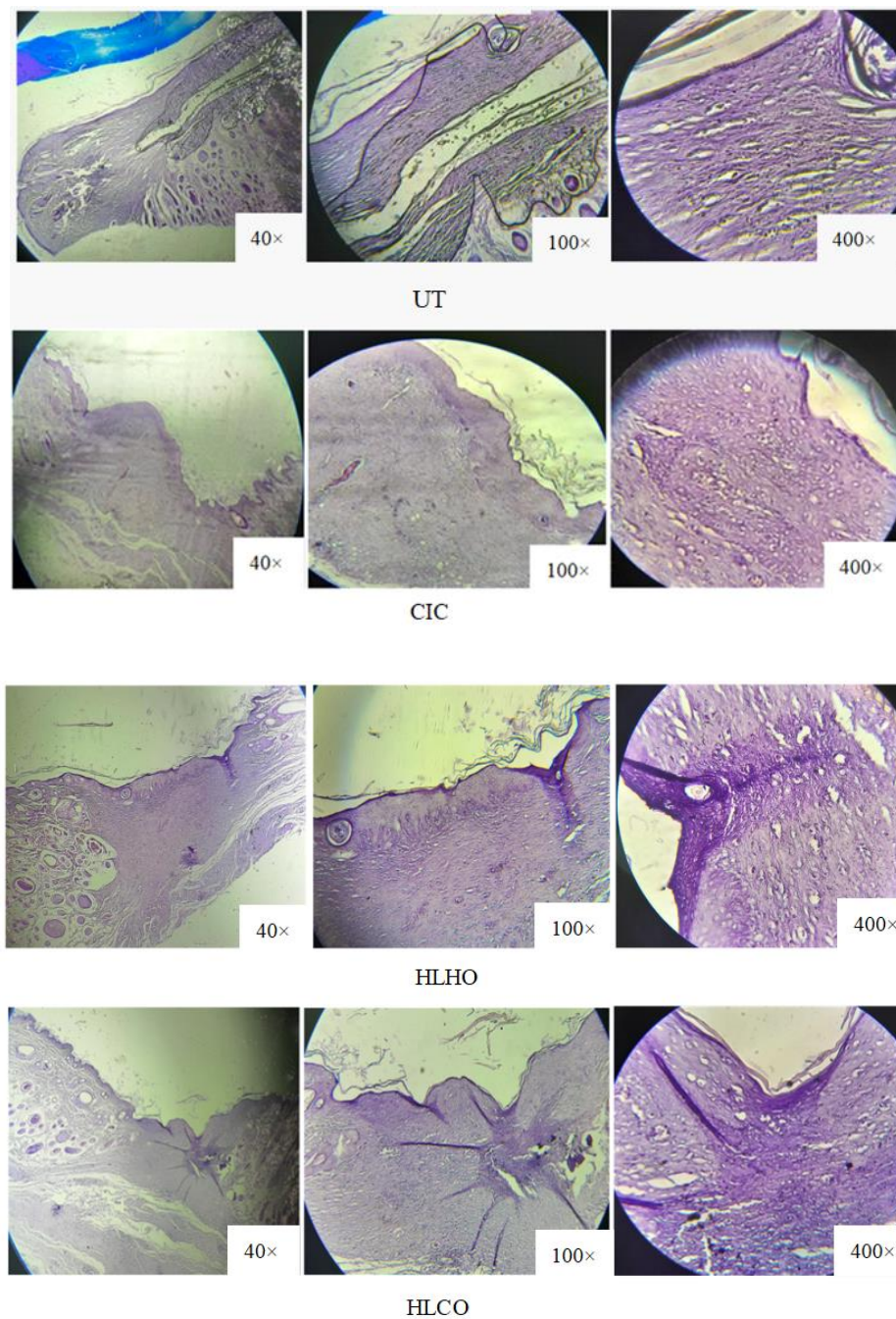


Figure 22: Histological evaluation of wound skin sections stained with hematoxylin and eosin (40 X, 100 X, 400 X magnification). UT group showed an inflamed dermis, incomplete epithelium, fewer collagen fibers and the presence of numerous inflammatory cells indicating incomplete wound healing. The three treated (CIC, HLCO and HLHO) showed better healing and re-epithelialization with a high epidermal thickness corresponding to hyperplasia and low inflammation.

Wounds can lead to serious complications, so rapid wound healing is essential to restore the disrupted anatomical stability and functional status of the skin. This rapid healing is only possible through rapid wound contraction, a short period of epithelialisation and an adequate increase in tensile strength (Lambebo et al., 2021).

All the studies of healing activity carried out to date in Algeria, and in many other Mediterranean area, have used mastic oils of coastal and near-coastal origin, most of which were hot extracted (traditional method). In the present study, excisional wound model was used to assess the wound healing effect of hot and cold extracted lentisk oils from the sub-arid Hodna region. In folk medicine, *P. lentiscus* oil, traditionally hot-extracted, is applied locally to wounds and burns. To date, no data have been reported on the healing properties of this sub-arid lentisk oil. Many studies have documented the ability of lentisk oils to treat wounds. Abdeldjelil (2016) found that lentisk oil, either alone or in combination with beeswax, had a significant therapeutic effect on albino Wistar rats' thermal burns. This remedy had a considerably better healing effect than silver sulfadiazine. Similarly, Maameri-Habibatni (2014) demonstrated that mastic oil and honey have healing properties on thermal burns by allowing the burn to tighten better during the proliferative and inflammatory phases.

According to a study by Djerrou et al. (2010), topical application of mastic oil to deep third-degree burns on New Zealand rabbits significantly accelerated the healing process. They demonstrated much better wound contraction and a shorter (30 days) healing duration. Just before, Boulebda et al. (2009) confirmed that mastic oil (from a coastal region), in particular its unsaponifiable fraction, is an active healing agent for excision wounds in rats. Furthermore, many plants rich in polyphenols are known to speed up the healing process (Guimarães et al., 2021). In fact, several phenolic compounds from different classes of polyphenols have healing properties (Mssillou et al., 2022).

The ability of HLCO and HLHO to heal wounds may be due to the presence of bioactive phytochemicals such as polyphenols, which are considered as multifunctional substances because of their diverse wound-healing capabilities as well as their antibacterial, antiproliferative, anti-inflammatory, antioxidant, and collagen-producing stimulants (Cedillo-Cortezano et al., 2024).

As we have shown, a total of twelve phenolic compounds were identified and quantified, which can be subdivided into three categories in descending order of abundance: catechin and

quercetin (7.99-1.43 mg/100g); sinapic acid, syringic acid, luteolin and gallic acid (0.95-0.34 mg/100g); apigenin, caffeic acid, myrectin and chlorogenic acid (0.13-0.06 mg/100g).

Numerous studies have demonstrated the value of catechin as an anti-inflammatory, antioxidant, and wound-care agent. Madhan et al. (2005) showed that the thermal stability of collagen increased by 10°C after treatment with catechin. It also improves the stability of collagen fibers treated with urea. More recently, Hu et al. (2024) showed that catechin stabilised collagen against collagenase attack. Quercetin treatment significantly improved wound healing by modulating cytokines and growth factors involved in the inflammatory and proliferative phases of wound healing (Gopalakrishnan et al., 2016, Choudhary et al., 2020). It also increased the production of collagen and fibronectin, which promoted faster wound healing (Gopalakrishnan et al., 2016).

Topical application of low-dose of sinapic acid may promote diabetic wound healing through its various bioactivities. Sinapic acid has shown improved recovery of re-epithelialisation and angiogenesis, increased collagen content and enhanced antioxidant capacity (Kaltalioglu, 2023). Similarly, Ren et al. (2019) showed that syringic acid could be used as a potential therapy for the treatment of diabetic wounds. Syringic acid increased faster wound closure and epithelialisation with increased hydroxyproline and protein levels, inhibition of the pro-inflammatory response (NF- κ B p65, TNF- α , IL-1 β , IL-8 and IL-2) with enhancement of the anti-inflammatory response (IL-10) and inhibition of increased oxidative stress. Luteolin increased the proliferation of fibroblasts, which then began to produce different types of collagen and fibronectin to form the first layer of the extracellular matrix (ECM). In addition, luteolin is able to inhibit the activity of hyaluronidase and collagenase, leading to a more stable ECM (Gendrisch et al., 2021). Gallic acid promotes wound healing in normal and hyperglucidic conditions by accelerating the migration of keratinocytes and fibroblasts and activating known wound healing factors (Yang et al., 2016).

Like others flavonoids and phenolic acids, apigenin, caffeic acid, myrectin and chlorogenic acid have previously been successfully tested as wound healing products. The improved healing activity of these compounds can be explained by various mechanisms: increasing capillary density and collagen production, repairing the epithelium, improving the collagen layer in the dermis and enhancing cell proliferation and wound contraction, as well as their antioxidant and anti-inflammatory effects (Bairagi et al., 2018, Yadav et al., 2022, Song et al., 2008, Elshamy et al., 2020, Bagdas et al., 2015).

Despite the different composition of HLHO and HLCO in phenolic compounds both qualitatively and quantitatively, and relying on literature data, treatment with the two oils showed similar healing activity comparable to the drug reference. These results suggest that the synergistic action of the different polyphenolics constituents may be mainly responsible for their healing properties. Hodna lentisk subarid oils significantly promotes the wound healing process by repairing the epithelium, improving the collagen layer in dermis and enhancing cell proliferation and wound contraction of wounds.

VIII. Molecular docking

Table 12 summarizes the interactions between the detected phenolic compounds and COX-2, along with the docking scores. Table 13 show the 2D and 3D molecular interactions. All compounds exhibited binding energies, ranging between (-6.2 kcal/mol) and (-8.6 kcal/mol). An effective ligand-target molecule interaction is indicated by a lower binding energy (a higher negative). The highest binding energy was recorded for Catechin (-8.6 kcal/mol), while the lowest binding energy (-6.2 kcal/mol) was recorded by syringic acid. Catechin exhibited encouraging results in this study due to its highest binding affinity of -8.6 kcal/mol and notable interactions with 10 amino acid residues surrounding the catalytic region. Luteolin (binding affinity: -8.0 kcal/mol) interacted with 11 amino acids, apigenin (binding affinity: -8.0 kcal/mol) interacted with 9 amino acids, chlorogenic acid (binding affinity: -7.9 kcal/mol) interacted with 4 amino acids, quercetin (binding affinity: -7.3 kcal/mol) interacted with 13 amino acids, myricetin (binding affinity: -6.7 kcal/mol), ferulic acid (binding affinity: -6.6 kcal/mol), caffeic acid (binding affinity: -6.4 kcal/mol), gallic acid (binding affinity: -6.4 kcal/mol), sinapic acid (binding affinity: -6.3 kcal/mol), p-coumaric acid (binding affinity: -6.3 kcal/mol), syringic acid (binding affinity: -6.3 kcal/mol) showed interaction with 8, 8, 8, 7, 4, 12, 8, and 10 amino acid residues, respectively.

Most of the ligands interacted with the amino acid residues in the selectivity pocket of COX-2. A variety of non-covalent hydrophobic interactions, including hydrogen bonds, carbon-hydrogen bonds, van der Waals, π - π T-shaped, π -sigma, π -Alkyl, and amide- π -stacked contacts, were also found. These interactions are crucial to the stability of complexes. Sinapic acid and ferulic acid formed the maximum number of hydrogen bonds established during the molecular docking study (3 bonds for each). The amino acid Arg120 was involved in hydrogen bond for the majority of compounds. It is worth to mention that the directionality

and specificity of an interaction, supplied by hydrogen bonds formed between a protein and chemical compounds, are essential elements of molecular recognition (Taidi et al., 2022).

Three compounds (catechin, apigenin, and luteolin) showed binding affinities that were equal to or higher than -8.0 kcal/mol. Catechin formed two hydrogen bond interactions with Arg120 and Met522 (distance = 2.80 Å and 2.72 Å, respectively); furthermore, it formed two π -sigma, π -Alkyl, and van der Waals interactions. Apigenin formed hydrogen bond interactions with Met522 (2.31 Å), π - π T-shaped, π -sigma, π -Alkyl and Amide- π -stacked. Similar interactions were seen for luteolin; in addition to hydrogen bond interactions with Arg120 (2.80 Å), a carbon hydrogen bond was formed with Arg120, four π -Alkyl interactions with Val523, Gly526, Leu531, Val116, two π -sigma interactions with Tyr355 and Gly526, π - π T-shaped interaction with Tyr355 and two amide- π -stacked with Gly526, Leu531.

The Root Mean Square Deviation (RMSD) values are critical for evaluating the convergence and reliability of the predicted ligand-protein binding poses (Bell and Zhang, 2019). For the vast majority of ligands, the rmsd/ub and rmsd/lb are 0.0. This result signifies a highly reliable and converged docking simulation, meaning the software found only one highly populated cluster or binding conformation. In essence, all predicted poses for these ligands (apigenin, catechin; chlorogenic, ferrulic, gallic, sinapic and syringic acids, luteolin and quercetin) were virtually identical to the best-scoring pose, lending high confidence to the reported Binding Affinity being associated with a single, clear, and stable binding mode. Conversely, the non-zero RMSD values for caffeic Acid, myricetin, and especially p-coumaric acid indicate that the docking simulation identified multiple distinct binding clusters (or poses) that are close in energetic score. The low RMSD for caffeic Acid suggests a minor structural variation in a secondary pose, but the high RMSD values for myricetin and p-coumaric acid strongly suggest that these molecules are likely able to bind to the protein in two or more widely separated or different orientations with similar predicted affinities.

Previous research has demonstrated that phenolic compounds, such as quercetin and luteolin, significantly inhibit COX-2 due to their strong binding affinities and interactions with essential amino acids in the active site of the enzyme (Paulino et al., 2016, Catarino et al., 2016).

The findings of this docking investigation suggest that the structural features of the components of lentisk oil, which have been shown to possess strong COX-2 inhibitory activity, are most likely responsible for their anti-inflammatory effects and binding abilities.

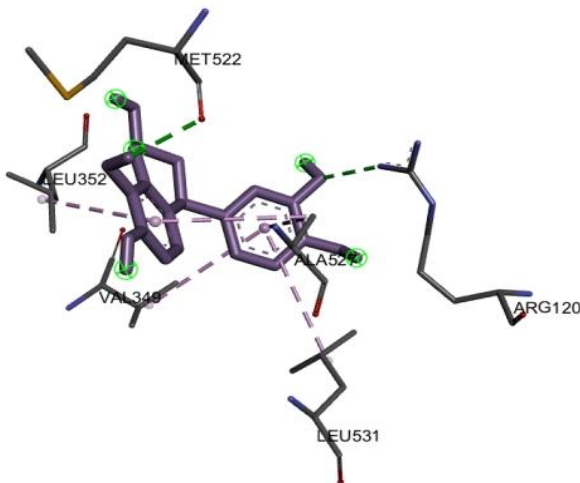
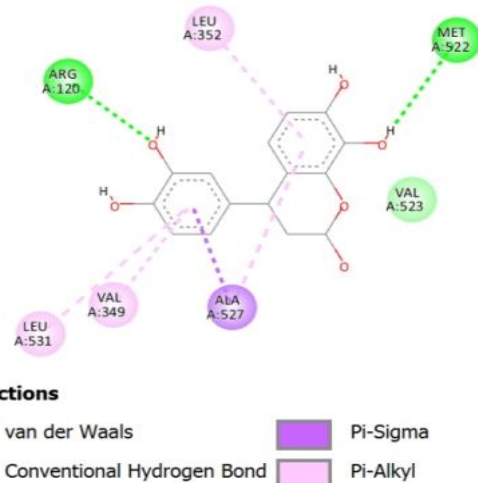
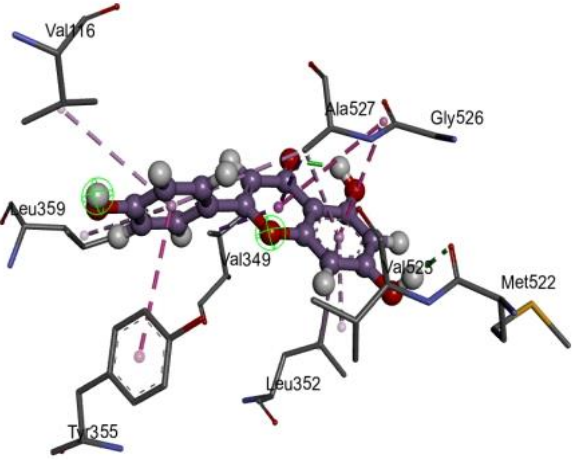
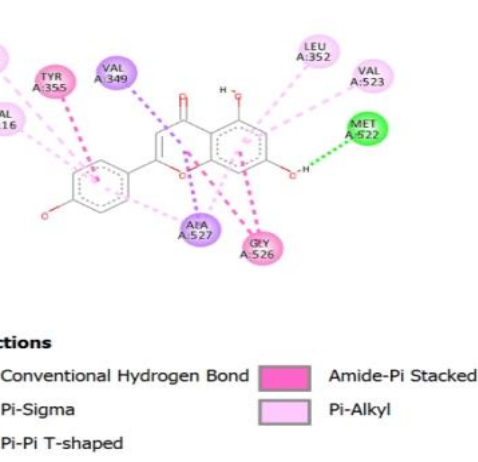
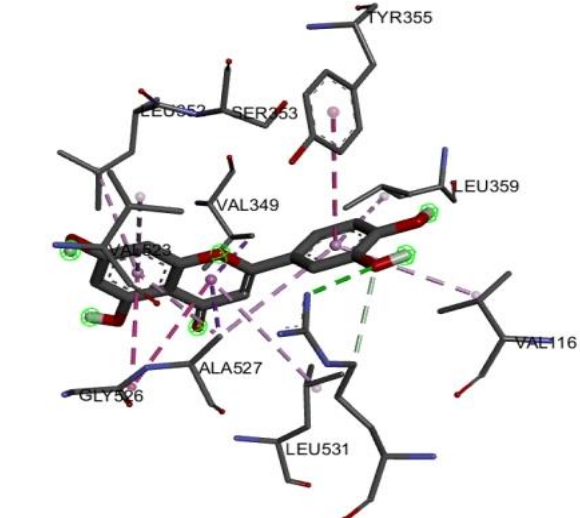
The selected substances may have a synergistic impact on COX-2 inhibition. These results provide valuable insights that may guide the discovery of patent COX-2 inhibitors for the treatment of inflammatory disorders.

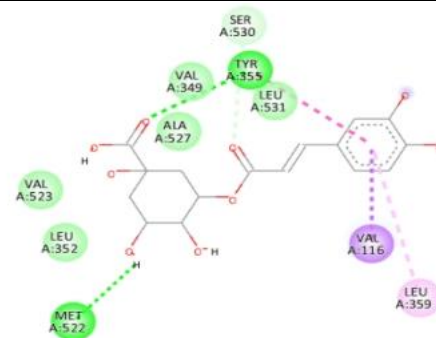
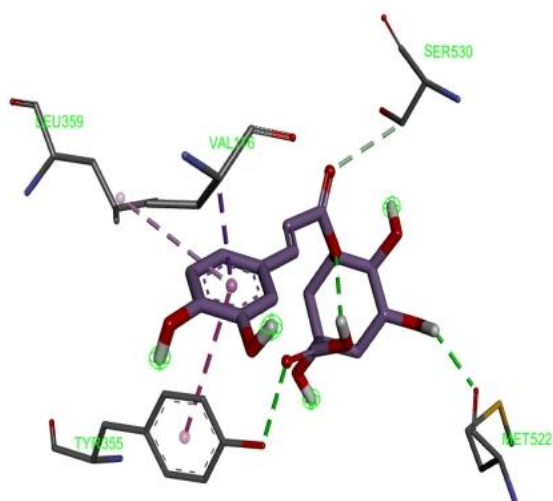
Table 12: Binding energy and molecular interactions of the ligands studied with COX-2 for anti-inflammatory activity.

Ligands	Binding energy (kcal/mol)	rmsd/ub	rmsd/lb	Hydrogen bonding (chain)	Distance (Å)	Other interactions
Catechin	-8.6	0.0	0.0	Catechin O....H....Arg120	2.80	π -sigma: Ala527
				CatechinO....H....Met522	2.72	π -Alkyl: Leu352, Leu331, Val349 Van der Waals: Tyr355, Val523, Ser353, Gly526
Apigenin	-8.0	0.0	0.0	Apigenin O....H....Met522	2.31	π -sigma: Ala527, Val349 π - π T-shaped: Tyr355 Amide- π -stacked: Gly526 π -Alkyl: Val532, Leu352, Leu359, Val116
Luteolin	-8.0	0.0	0.0	Luteolin O....H....Arg120	2.80	Carbon hydrogen bond: Arg120 π -sigma: Tyr355, Gly526 π -Alkyl: Val523, Gly526, Leu531, Val116 π - π T-shaped: Tyr355 Amide- π -stacked: Gly526, Leu531
Cholorogenic acid	-7.9	0.0	0.0	CholorogenicO...H....Tyr355	3.21	Carbon hydrogen bond: Ser530
				CholorogenicO...H....Met522	2.33	π -sigma: Val116 π - π T-shaped: Tyr355 π -Alkyl: Val116
Quercetin	-7.3	0.0	0.0	Quercetin O....H....Arg120	2.90	π -sigma: Leu352
				Quercetin O....H....Tyr385	2.26	π - π T-shaped: Tyr355 Amide- π -stacked: Gly526 π -Alkyl: Ala527, Val523, Val349, Leu359 Van der Waals : Phe381, Phe518,

						Leu531, Val116
Myricetin	-6.7	3.27	1.318	MyricetinO....H....Arg120 Myricetin O....H....Gly526	2.80 1.92	Carbon Hydrogen Bond : Ser353 π -sigma: Leu352 π - Alkyl: Leu531, Val523, Ala527, Val349
Ferulic acid	-6.6	0.0	0.0	Ferulic O....H....Tyr355 Ferulic O....H....Tyr385 Ferulic O....H....Ser530	3.14 2.94 3.12	Van der Waals : Met522, Leu359, Val116 π -Alkyl: Tyr355 Alkyl: Met522 π -sigma: Val349, Ala527
Caffeic acid	-6.4	1.037	0.94	Caffeic acid O....H....Tyr355 Caffeic acid O....H....Arg120	2.19 3.24	Carbon hydrogen bond: Ser353 Amide- π -stacked: Gly526 π -Alkyl: Val523, Leu352, Ala527
Gallic acid	-6.3	0.0	0.0	Gallic O....H....Gly526	2.30	Carbon Hydrogen Bond: Ser353, Gly526 π -sigma: Leu352 π -Alkyl: Val523
P-coumaric acid	-6.3	5.829	1.858	P-oumaric O....H....Tyr355	3.01	Van der Waals: Arg120, Val349, Met522 Amide- π -stacked: Gly526 π -Alkyl: Val523, Leu352, Ala527
Sinapic acid	-6.3	0.0	0.0	Sinapic O....H..... Tyr355 Sinapic O....H.....Tyr385 Sinapic O....H..... Ser530	3.30 2.96 3.09	Carbon Hydrogen Bond : Leu352 π -sigma: Ala527, Val349 Alkyl : Leu531 π -Alkyl: Val116, Val523, Leu359 Van der Waals: Arg120, Gly526
Syringic acid	-6.2	0.0	0.0	Syringic O....H..... Leu352 Syringic O....H.....Gly526	2.22 2.26	Carbon Hydrogen Bond: Ser353, Ser530, Met522 Van der Waals: Tyr355 π -sigma: Leu352 Alkyl: Ala527, Val349 π -Alkyl: Trp 387

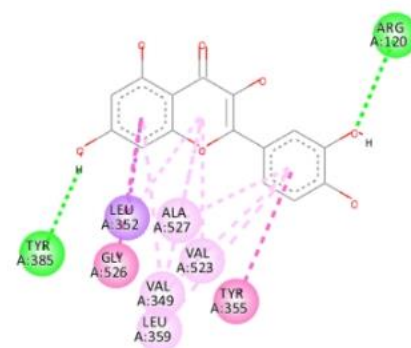
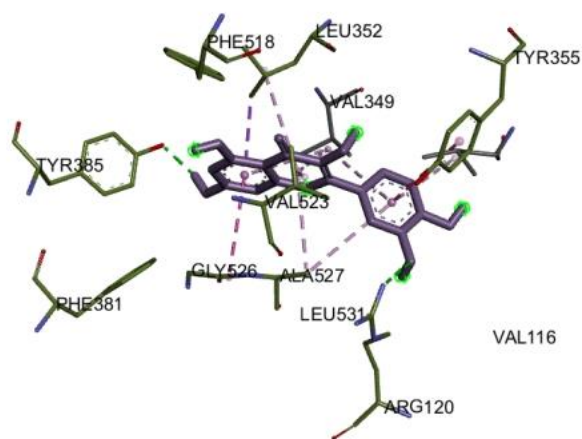
Table 13: Molecular interaction between detected phenolic compounds and COX-2: 2D and 3D structure interaction.

Ligand	3D receptor binding	2D receptor binding
Catechin		
Apigenin		
Luteolin		

Chlorogenic
acid**Interactions**

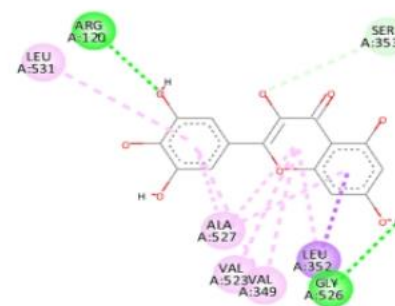
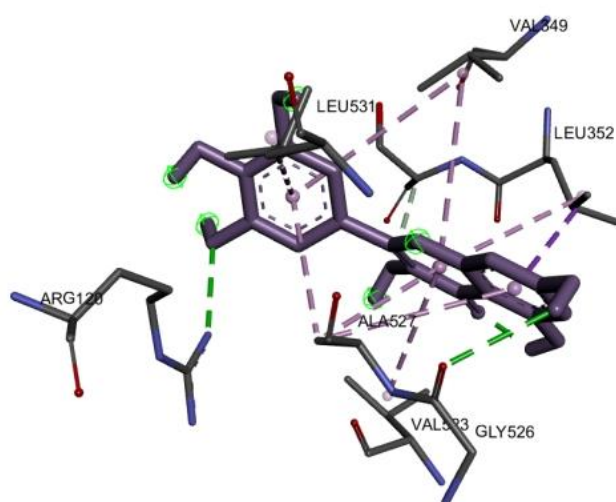
	van der Waals		Pi-Sigma
	Conventional Hydrogen Bond		Pi-Pi T-shaped
	Carbon Hydrogen Bond		Pi-Alkyl

Quercetin

**Interactions**

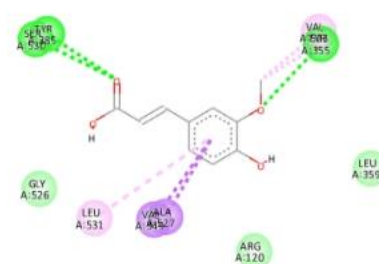
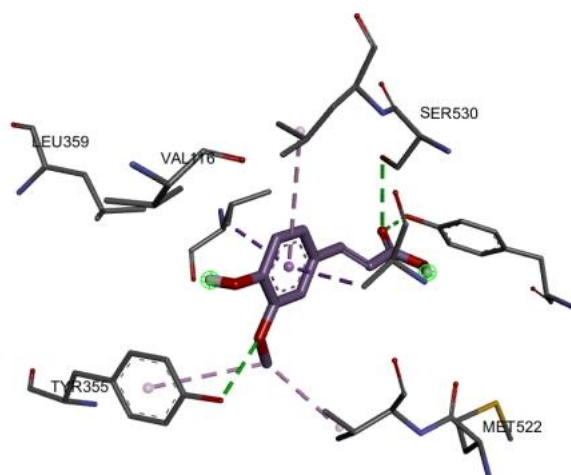
	Conventional Hydrogen Bond		Amide-Pi Stacked
	Pi-Sigma		Pi-Alkyl
	Pi-Pi T-shaped		

Myricetin

**Interactions**

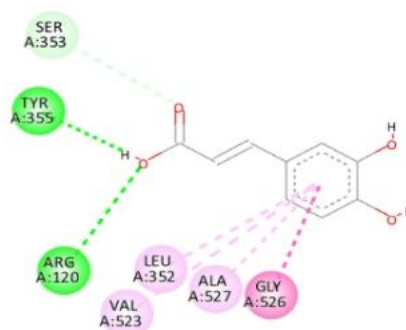
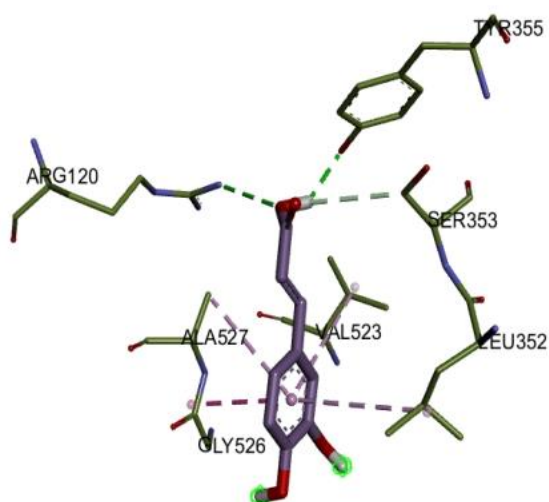
	Conventional Hydrogen Bond		Pi-Sigma
	Carbon Hydrogen Bond		Pi-Alkyl

Ferulic acid

**Interactions**

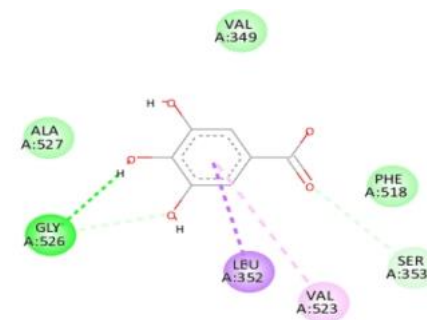
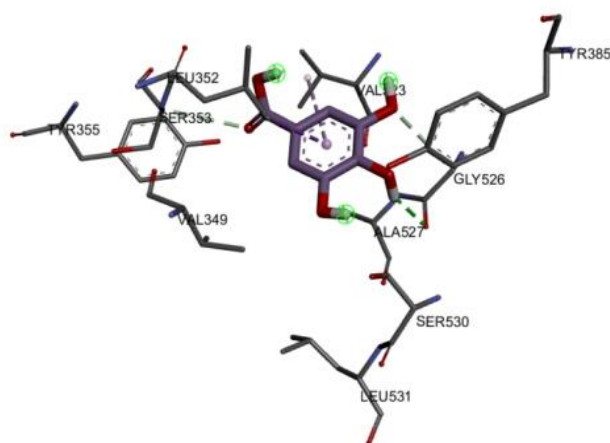
van der Waals	Alkyl
Conventional Hydrogen Bond	Pi-Alkyl
Pi-Sigma	

Caffeic acid

**Interactions**

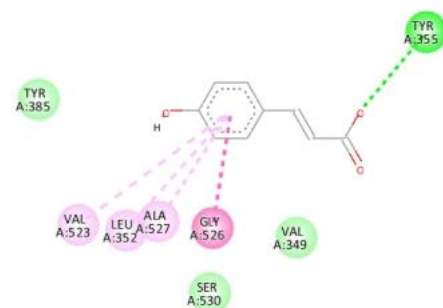
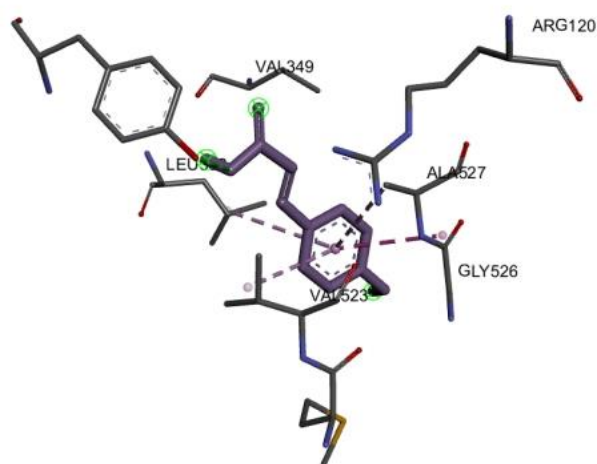
Conventional Hydrogen Bond	Amide-Pi Stacked
Carbon Hydrogen Bond	Pi-Alkyl

Gallic acid

**Interactions**

van der Waals	Pi-Sigma
Conventional Hydrogen Bond	Pi-Alkyl
Carbon Hydrogen Bond	

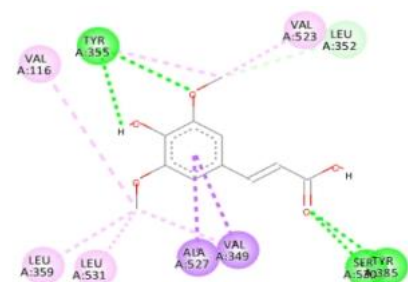
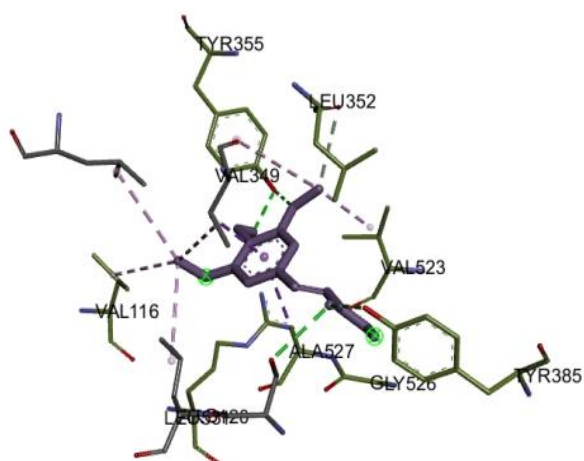
P-coumaric
acid



Interactions

	van der Waals		Amide-Pi Stacked
	Conventional Hydrogen Bond		Pi-Alkyl

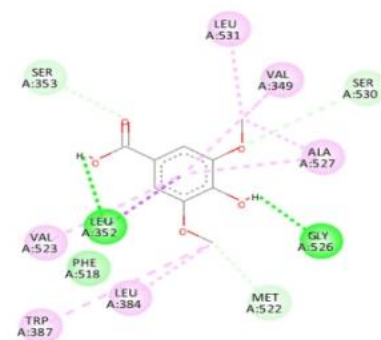
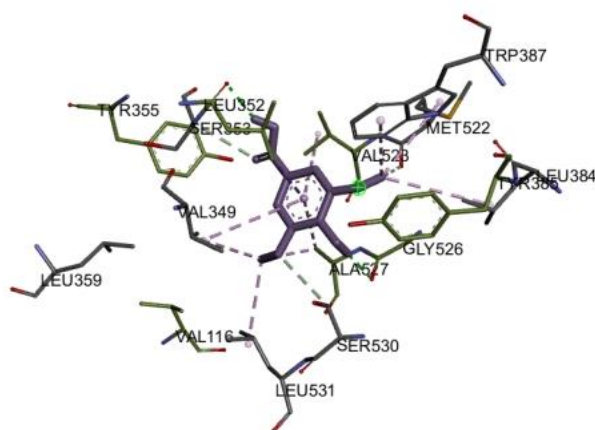
Sinapic acid



Interactions

	Conventional Hydrogen Bond		Alkyl
	Carbon Hydrogen Bond		Pi-Alkyl
	Pi-Sigma		

Syringic acid



Interactions

	van der Waals		Pi-Sigma
	Conventional Hydrogen Bond		Alkyl
	Carbon Hydrogen Bond		Pi-Alkyl

Conclusion

Conclusion and perspectives

The choice of *Pistacia lentiscus* seed oil was made on the basis of its use in traditional medicine and its wealth in bioactive compounds. Furthermore, according to the bibliography consulted, no work has been carried out on the Hodna sub-arid region oil. This led us to study this oil in terms of physicochemical properties, phytochemical composition, toxicity, and pharmacological activity.

Extraction of fixed oils from *P. lentiscus* fruits from the Hodna sub-arid region has been obtained by hot (traditional method) and cold extraction. Miscellaneous physicochemical parameters and phytochemical composition were influenced by the sub-arid origin of *P. lentiscus* and the extraction method, including fatty acids, polyphenol compounds, and tocols. The following conclusions may be drawn: cold extraction exhibited a notably higher oil yield compared to hot extraction. There were noticeable differences in the color, density, refractive index, acidity, peroxide value, iodine value, saponification index, and K232 extinction value of the cold and hot lentisk seed oils, varying depending on the extraction process.

Both oils, and more specifically HLCO, were rich in unsaturated fatty acids like linoleic acid and oleic acid, with the latter serving as the main fatty acid.

Both qualitatively and quantitatively, phenolic compounds were more abundant in HLCO than HLHO. Seven compounds in HLHO were determined with quercetin and sinapic acid dominating, and nine compounds in HLCO with catechin and quercetin dominating. Notably, four phenolic compounds were found in the oils under study for the first time: catechin, myricetin, and chlorogenic acid for HLCO, and sinapic acid for HLHO. These compounds can be thought of as markers unique to the fixed oils of Hodna lentisk seeds.

Regarding tocol levels, HLHO and HLCO were shown to be plentiful in vitamin E, with high concentrations of tocopherols such as α - and γ -tocopherol. Furthermore, whereas both oils had significant scavenging capacities, their antibacterial and antifungal properties were quite weak.

Finally, the two oils showed similar healing activity with results comparable to Cicatryl Bio. Additionally, the molecular docking study revealed that the phenolic compounds in this oil have a significant inhibitory effect on COX-2, indicating that this oil may have anti-inflammatory properties.

The findings of this study have unveiled a number of intriguing characteristics of the *Pistacia lentiscus L.* seed oil from the sub-arid region of Hodna. This oil offers a natural source of bioactive compounds that have potential uses in the food, cosmetics, and health sectors. It can also be incorporated into new products or used to replace synthetic compounds.

The results of this investigation can serve as a reference for the utilization of this oil as a source for cosmetic, medicinal, and feed applications. Further research to develop the antiinflammatory action in vivo would be highly intriguing. It would also be good to purify and identify the oil's bioactive compounds. Furthermore, it would be desirable to create a pharmaceutical formulation based on this oil.

Annexes

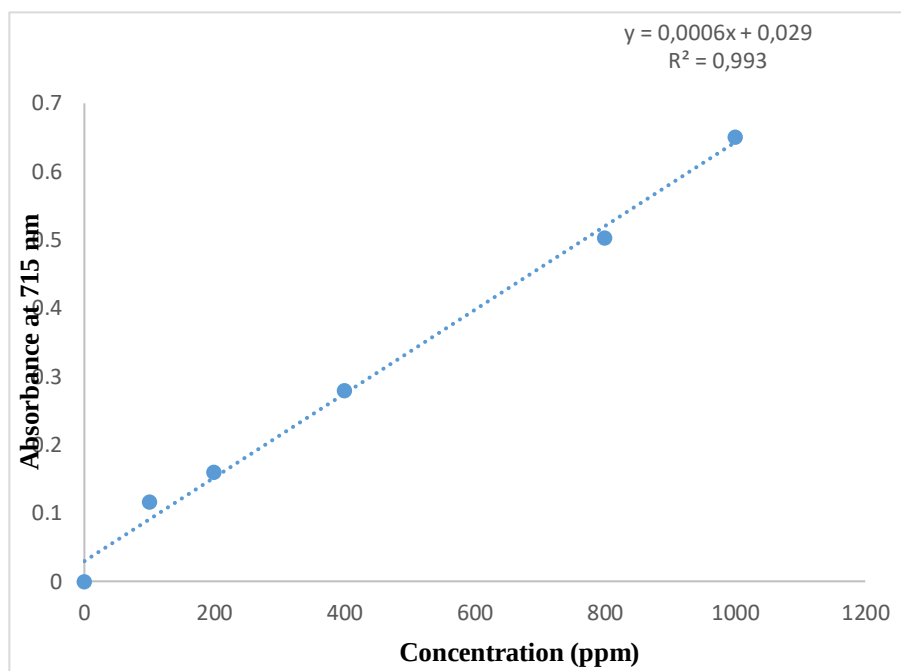
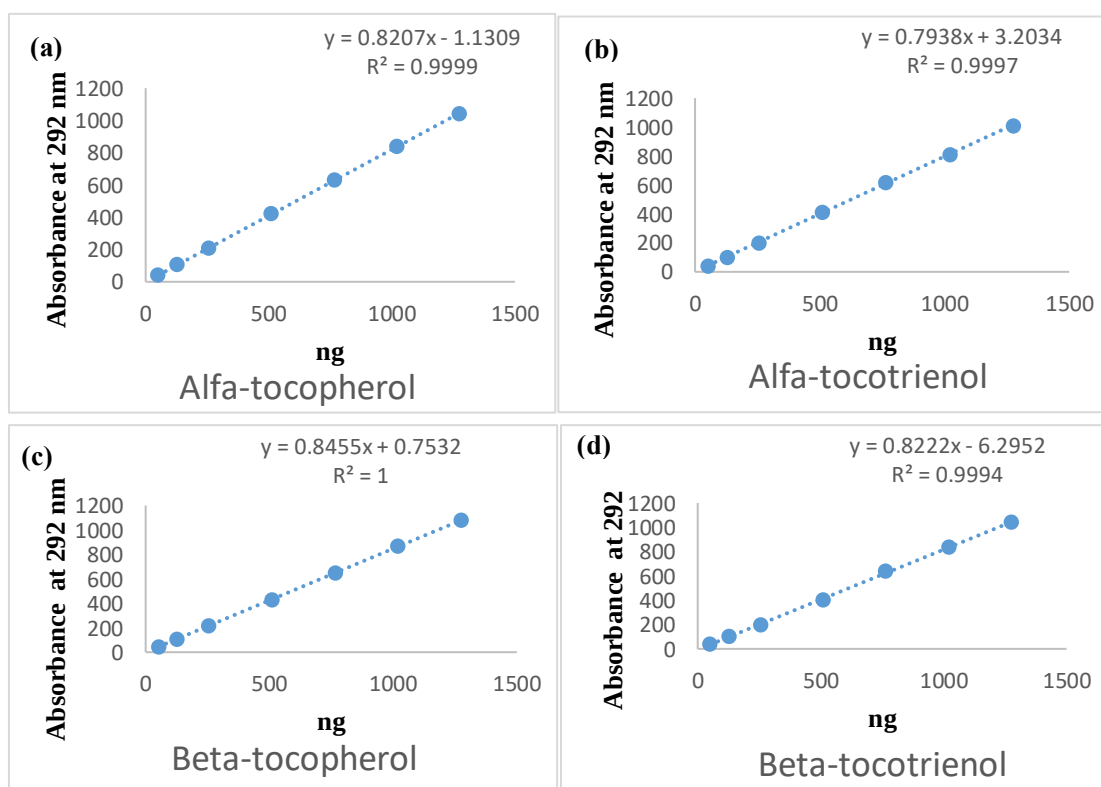


Figure 1: Calibration curve of gallic acid.



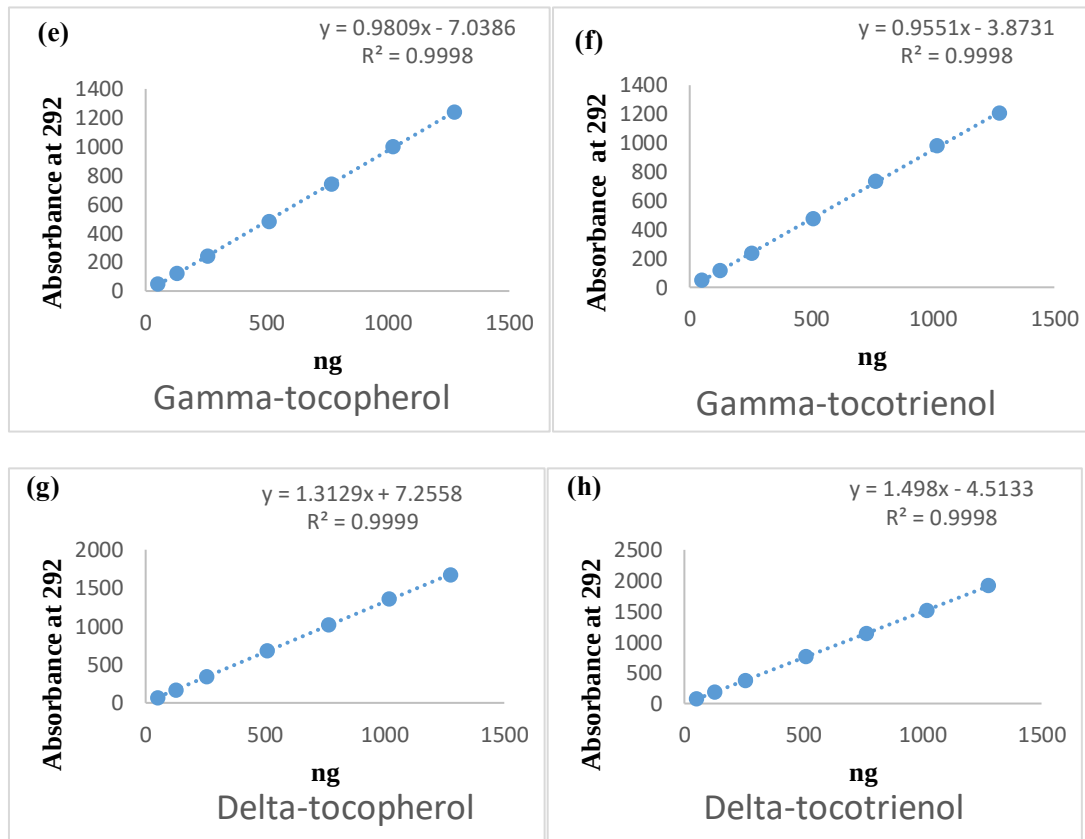


Figure 2: Calibration curves of tocopherols: (a) alfa-tocopherol, (b) Alfa-tocotrienol, (c) Beta-tocopherol, (d) Beta-tocotrienol, (e) Gamma-tocopherol, (f) Gamma-tocotrienol, (g) Delta-tocopherol, (h) Delta-tocotrienol.

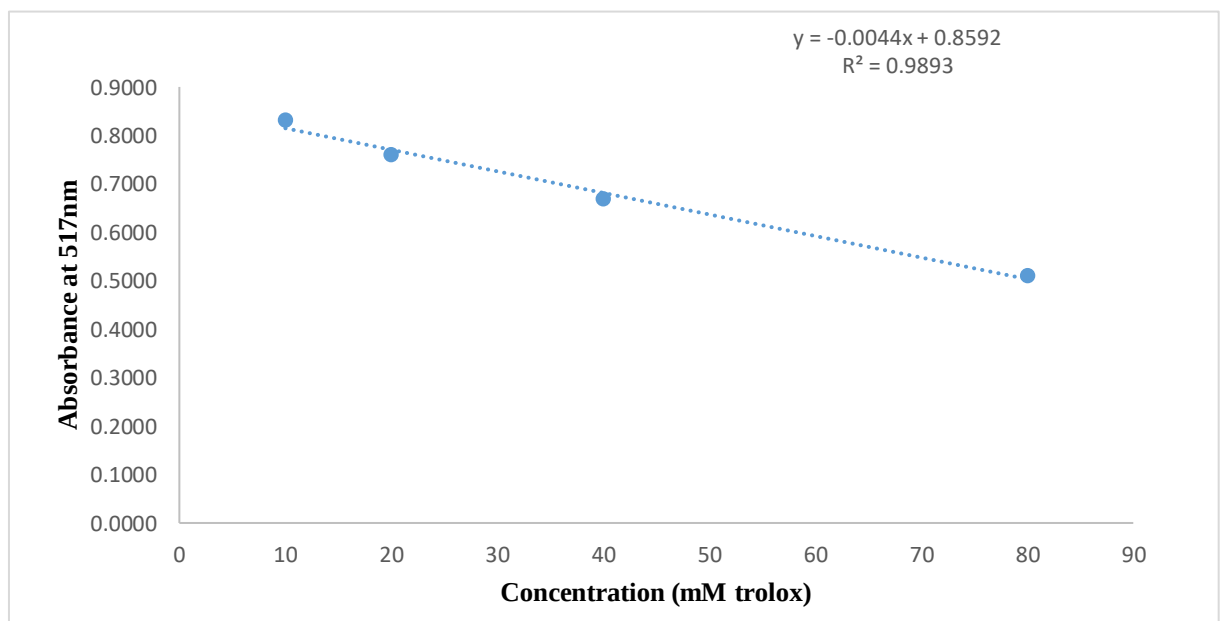


Figure 3: Trolox calibration curve

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