Prominent Pharmacological Activities of *Pistacia lentiscus* Polyphenols

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Pistacia lentiscus (lentisk) is a plant species of the Anacardiaceae family. It is a medicinal plant that grows wild in the Mediterranean region. The plant *P. lentiscus*, which is used in traditional medicine, possesses pharmacological attributes and may offer significant potential as a therapeutic agent. The biological and therapeutic potentials of lentisk extracts have been evaluated in terms of antioxidant, antimicrobial, and anti-inflammatory activities. Most of these activities are related to the phenolic composition of this plant. It has been used in traditional medicine for the treatment of several diseases, such as for gastrointestinal diseases, eczema, and throat infections, due to its potent antioxidant, anti-inflammatory, and antimicrobial effects.

Pistacia lentiscus | polyphenols | phenolic acids | flavonoids

1. Antioxidant Activity

Different methods were used to evaluate the antioxidant capacity of phenolic extracts of *P. lentiscus*: DPPH (2,2-diphenyl1-picrylhydrazyl), i.e., free radical scavenging activity; free hydroxyl radicals (HO); ferric-reducing power (FRAP); the carotene bleaching (CB) assay; the oxygen radical absorbance capacity (ORAC) test; hydrogen peroxide scavenging activity (H_2O_2); the phosphomolybdenum (TAC) assay; and the ABTS·+: 2,2′-azino-bis-(3 ethylbenzthiazoline-6-sulphonic acid) assay were the most used (**Table 1**). These methods have different modes of action. Electron transfer, proton transfer, and iron reduction are the main mechanisms involved. The observations noted after the evaluation of the antioxidant potential of this plant are illustrated in **Table 1**. Investigations (**Table 1**) were conducted regarding the evaluation of antioxidant activity by comparing to reference antioxidants (ascorbic acid, gallic acid, trolox, rutin, and quercetin). The results of these investigations revealed that lentisk's antioxidant properties are comparable to those of the reference antioxidants. The extracts of *P. lentiscus* remain a considerable source of natural antioxidants.

The ability of the *P. lentiscus* extracts to prevent free radicals could be attributed to the high content of phenolic compounds [1][2][3][4]. There is a significant positive correlation between the antioxidant test results and the amount of total phenols [5]. The antioxidant capacity of *P. lentiscus* extract has been shown to be due primarily to gallic acids and their galloyl derivatives (5-Ogalloyl; 3,5-O-digalloyl; 3,4,5-tri-O-galloyl) [1]. The trapping of DPPH increases accordingly with the number of galloyl groups [1]. Quercetin and gallic acid are powerful natural antioxidants [1], and monophenols are less effective than polyphenols [6][7]. With gallic acid, the inductive effect of these three hydroxyl groups is a significant factor influencing the increase in antioxidant activity [6]. This suggests that they are partly responsible for the antiradical potential observed in the lentisk extracts [8]. In addition, the

antioxidant activity also depends on the polarity of the solvent, the solubility of the phenolic compounds, and the hydrophobic nature of the reaction medium [9]. A high polarity of the extract solvent increases the antioxidant capacity (DPPH and FRAP) of the lentisk extracts. Polar extracts such as ethanol, methanol, and aqueous extracts were found to be rich in polar compounds, which are either hydrogen atom donors or singular atom transfer agents [9]. In addition to the solvent polarity, the solubility of the phenolic compounds is governed by the degree of polymerization of the phenols, the part of the plant used, and the variability of soil and climatic conditions [10][11]. The flavonol glycosides found in lentisk [8][12][13] are known for their antioxidant attributes, which are strongly related to their structural characteristics, i.e., the hydrogen donor substituents (OH groups) and the presence of a 2,3 double bond that increases their scavenging capacity and inhibition of pro-oxidant enzymes [14]. It has been shown that the main compound present in lentisk extracts, i.e., myricetin-rhamnoside [8][12], has a DPPH scavenging capacity comparable to that of vitamin C [15].

Table 1. Pharmacological activities of lentisk phenolic extracts.

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
Antioxidant activity	Leaves	Ethanolic extract from leaves	DPPH (2,2-diphenyl-1-picrylhydrazyl): free radical scavenging activity	The extract (3 g/L) inhibited 95.69% of the activity of the DPPH radicals	[1]
	Leaves	Dichloromethane extract Ethylacetate extract Ethanol extract Methanol extract Aqueous extract	DPPH free radical scavenging activity Ferric-reducing activity power (FRAP) Carotene bleaching (CB) assay	IC50 = 05.44 (µg/mL) (Ethanolic extract) 309.60 mg ascorbic acid equivalent/g extract (methanolic extract) Inhibition = 90.32% per 2 g/L of extract (dichloromethane extract)	[9]
	Leaves	Ethanolic extract	Oxygen radicalabsorbance capacity(ORAC) test	Antioxydant capacity = 5865 µmol TE/100 gE	[8]
	Leaves	Aqueous extract	Free radical scavenging activity (DPPH assay) Hydrogen peroxide scavenging activity (H_2O_2) Ferric-reducing power (FRAP) assay Antioxidant assay by phosphomolybdate method	IC50 (aqueous extract) = 9.86 µg/mL	[16]

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
	Berries	Ethanolic extract	DPPH assay (ABTS·+: 2,2′-azino-bis-(3 ethylbenzthiazoline-6-sulphonic acid)) assay Reducing power activity assay	IC50 = 8.60 mg/mL IC50 = 8.65 mg/mL IC50 = 12.21 mg/L	[17]
	Leaves	Methanolic extract	DPPH assay β-carotene bleaching test	IC50 = 0.008 mg/mL IC50 = 0.12 mg/mL	[3]
	Leaves	Aqueous fraction obtained from chloroformic extract	Reducing power assay Scavenging ability against DPPH radical Activity against linoleic acid peroxidation	IC50 = 50.03 lg/mL IC50 = 4.24 lg/mL IC50 = 0.82 lg/mL	[18]
	Leaves	Methanolic fraction from chlorformic extract	DPPH assay ABTS assay	inhibition of 50% of DPPH radicals (2.9 µg/mL extract) inhibition of 50% of ABTS•+ (0.6 µg/mL extract)	[19]
	Fruits	Aqueous extract Ethyl acetate extract Butanol extract	Free radical scavenging (DPPH assay)	100 mg/mL of aqueous extract inhibited 86.13% of DPPH radicals	[20]
	Leaves	Ethyl acetate fraction from ethanolic extract	Ferric-reducing power assay (FRAP)	IC50 = 15.0 µg/mL (FRAP)	[4]
	Fruits	Phenolic extract from vegetable oil	DPPH assay	Significant antioxidant power (IC50 = 37.38 mg/mL)	[21]
	Fruits Twigs Leaves	Aqeuous extract Hexane extract Ethyl acetate extract Methanol extract	Phosphomolybdenum (TAC) assay	The aqueous extract of *P. lentiscus* leaves showed the highest TAC with 488.16 mg AA/g of extract.	[5]

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
		Ethanol extract			
	Leaves Fruits	Methanolic extracts	Free radical DPPH assay	EC 50 = 0.121 mg/mL for leaves and EC 50 = 0.26 mg/mL for fruits	[22]
	Aerial parts	Methanolic extract	FRAP	reducing power = 84.6–131.4 mmol Fe2+/L plant extract	[23]
Antibacterial activity	Leaves	Dichloromethane extract Ethylacetate extract Ethanolic extract Methanolic extract Aqueous extract	The disk diffusion method on Muller–Hinton agar (MHA).	All these extracts had efficient antimicrobial activity against: Gram-positive bacteria: *Micrococcus luteus*, *bacillus subtilis*, and *listeria innocua* Gram-negative bacteria: *Escherichia coli* The activity was almost the same for all the extracts against each bacterium	[9]
	Leaves	Aqueous extract	The disc diffusion method	A maximum inhibition zone of 12 mm was observed on *Pseudomonas aeruginosae*, while moderate activity was obtained against all strains	[16]
	Leaves	Decoction Petroleum ether extract Ethanol extract Maceration Infusion	The minimal inhibitory concentration (MIC) was determined by a microdilution assay in microtiter plates The minimal bactericidal concentration (MBC) was determined by carrying out a subculture of the tubes showing no growth on plates	Antimicrobial activity against: *Staphylococcus aureus* and *Escherichia coli* Decoction showed the best activity (MIC = 312 mg/L for all the three bacterial strains). MIC and MBC values were the same, so the substances should	[24]

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
				possess bactericidal activity	
	Leaves	Ethyl acetate fraction from ethanolic extract	The MIC of the extract was determined using the agar dilution method The MBC was determined by taking samples from the nutrient agar plates that showed no visible growth after 24 h incubation and subculturing them in tubes containing nutrient broth	Moderate inhibitory activities against: *Staphylococcus aureus*, *Listeria innocua*, *Bacillus cereus*, *Escherichia coli*, *Salmonella typhi*, *Salmonella enterica*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Vibrio cholerae*, and *Enterococcus faecalis* There was remarkable activityagainst *Vibrio cholerae* with an MBC value of 0.3 mg/mL	[4]
	Leaves	Methanolic extract Aqueous extract	The disk diffusion method	Antibacterial activity against: *Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Pseudomonas aeruginosa*, and *Proteus mirabilis* Methanol extract showed a significant inhibitory effect on the growth of all tested bacterial isolates, with 33 mm and 27 mm against *S. aurous* and *S. haemolyticus*, respectively	[25]
Antifungal activity	Leaves	Dichloromethane extract Ethylacetate extract Ethanolic extract Methanolic extract Aqueous extract	The disk diffusion method on Muller–Hinton agar (MHA).	Significant antifungal activity against: *Candida pelliculosa* and *fusarium oxysporum albidinis* The ethanolic extract was the most active	[9]

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
	Leaves	Hydro-methanolic extract (70/30 *v*/*v*)	Diffusion using solid medium method	The extract was more active against *Trichophyton mentagrophyte* and *Microsporum canis*, with growth inhibition: *Trichophyton mentagrophyte* (17 mm) *Microsporum canis* (16.7 mm)	[26]
	Leaves	Aqueous extract	The minimal inhibitory concentration (MIC) was determined by a microdilution assay in microtiter plates	Antifungal activity against: *Candida albicans*, *Candida parapsilosis* and *Cryptococcus neoformans* The highest activity of *P.lentiscus* was against *T. glabrata* (MIC = 39–156 mg/L)	[24]
	Leaves	Ethyl acetate fraction from ethanolic extract	The MIC of the extract was determined using the agar dilution method	Good antifungal activity against *Candida albicans* with CMI 0.1 mg/mL	[4]
Anticancer activity	Leaves	Ethanolic extract	The in vitro cytotoxicity of the extract was determined by sulforhodamine B (SRB) assay	Moderate cytotoxic activity against lung cancer A549, breast cancer MCF7, prostate cancer PC3, and HepG2 liver cancer	[27]
	Leaves	Ethanolic extract	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide (MTT) assay	Anticancer potential against melanoma (B16F10) cell lines	[8]
	Leaves	Methanolic fraction from chlorformic extract (sonication)	MTT, SRB, and LDH assays forSH-5YSY, and SK-N-BE(2)-C human, and neuronal cell lines, and also on C6 mouse glial cell line	Significant cytoprotective response in both the oxidized cell systems	[19]
	Edible fixed	Hydro-methanolic extract (methanol	A crystal violet viability assay with increasing	The extract induced clear dose-dependent	[28]

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
	oil (fruits)	80%, *v*/*v*)	concentrations was carried out	effects on the growth of the HT-29 cell line derived from human colorectal adenocarcinoma	
	Leaves	Hydro-methanolic extract (8:2 *v*/*v*)	Cell viability by MTT assay	The extract showed activity on: the SK-N-BE(2)C cell line with an IC50 value of 100.4 ± 1.6 µg/mL the SH-SY5Y cell line with IC50 value of 56.4 ± 1.1 µg/mL	[29]
Anti-inflammatory activity	Leaves	Ethanolic extract	The measurement of the secretion of interleukin-1 by macrophages exposed to ATP or H_2O_2 on the THP-1 monocytic cell line	Significant anti-inflammatory activity	[9]
	Leaves	Methanolic extract	Albumin denaturation inhibition method in human red blood cell suspension	Apparent anti-inflammatory activity	[30]
	Leaves	Chloroformic extract Ethyl acetate extract Methanolic extract	The carrageenan-induced paw edema assay	MeOH extract presented the best anti-inflammatory activity Dose of 200 mg/kg showed 68% edema inhibition	[31]
[9]	Leaves	Methanolic extract (maceration) Aqueous extract (decotion) [24]	Three inflammation models: Croton oil-induced ear edema in mice Carrageenan induced-pleurisy in rats Acetic acid-induced vascular permeability in mice [11]	Local treatment with 2 mg/ear of: alcoholic extract significantly decreased ear edema (65%) aqueous extract exerted a lower inhibitory effect (51%). methanolicand aqueous extracts: at (400 mg/kg) inhibited neutrophil migration by 29% and 38%, respectively; [4]	[32] [9]

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methanolic extract showed a higher zone of inhibition than that of the aqueous extract. The maximum zone of inhibition was observed in the methanolic extract at 100% concentration with 33 mm and 27 mm against *S. aureus* and *S. haemolyticus*, respectively [25]. *P. aeruginosa* was of particular interest, as this bacterium was inhibited by

Pharmacological Activity	Plant Part	Product	Method	Significant Results)	Ref
				at methanolic and aqueous extracts (100 µg/mL) inhibited neutrophil chemataxis by 81% and 71%, respectively	[25] [34] [35]
	Fruits	Acetonic extract	The ear edema model induced by Croton oil and the airpouche model induced by lambda carrageenan	Oral administration dose of 300 mg/Kg of extract decreased ear edema by 80% Dose of 1 mg of extract/pouche decreased pouch edema by 34%	[4] [33] [36] [37] [38]

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Some studies (**Table 1**) aimed to evaluate the anticancer potential of different phenolic extracts of this plant in vitro. The ethanolic leaf extracts showed anticancer potential against lung cancer A549, breast cancer MCF7, prostate cancer PC3, and HepG2 liver cancer in vitro [27]. Yemmen et al. (2017) [28] revealed the anti-proliferative activities of leaf hydro-methanolic extracts against two human neuroblastoma cell lines (SK-N-BE(2) C and SH-SY5Y) with IC50 values of 100 µg/mL and 56 µg/mL, respectively. The anticancer potential of the crude extracts against melanoma (B16F10) and breast (EMT6) cell lines was also evaluated. The leaf and fruit extracts inhibited the growth of B16F10 cells (IC50 = 56 and 58 µg/mL, respectively) [9].

MTT: 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2Htetrazoliumbromide; SH-SY5Y: neuroblastoma cells were purchased; SK-N-BE(2)-C: human bone marrow neuroblastoma cells; SRB: sulforhodamine B.

Phytochemical studies have indicated the presence of significant amounts of flavonoids, tannins, and phenolic compounds in *P. lentiscus* extracts [14], which may be responsible for the anticancer activity of lentisk extracts. It has been shown that the presence of a 2,3-double bond and three adjacent hydroxyl groups in the structure could confer a higher anticancer potential to a flavonoid [39]. One example of the flavnoids found in lentisk extracts is myricetin; this molecule was found to have significant cytotoxic activity against B16F10 melanoma cell cultures [39].

4. Anti-Inflammatory Activity

P. lentiscus is used in traditional medicine for the treatment of inflammation, burns, and gastrointestinal disorders. Anti-inflammatory activity has been the focus of many recent investigations (**Table 1**). Dellai et al. (2013) [31] examined the efficacy of aqueous and organic extracts of *P. lentiscus* leaves in vivo for their anti-inflammatory and anti-ulcerogenic activities using the carrageenan-induced paw edema assay and HCl/ethanol-induced gastric injury in rats, respectively. Aqueous (AQ), chloroformic ($CHCl_3$), ethyl acetate (EtOAc), and methanolic (MeOH) leaf extracts administered intraperitoneally showed a dose-dependent anti-inflammatory effect. Leaf extracts of $CHCl_3$, EtOAc, and MeOH, administered orally, showed concentration-dependent inhibition of gastric lesions. The effect of all the extracts in both activities is comparable to the reference drugs: cimetidine and acetylsalicylate of lysine, respectively [31]. The pharmacological evaluation of the *P. lentiscus* leaf extracts showed the anti-inflammatory potential of this plant and that its activity is unlike non-steroidal anti-inflammatory drugs and corticosteroids. The

extracts did not cause damage to the stomach mucosa but showed an inhibition of lesion formation. The work carried out by Bouriche et al. (2016) [32] concerns the measurement of the anti-inflammatory activity of alcoholic and aqueous extracts of *P. lentiscus* leaves. Croton oil-induced ear edema in mice was used as a model of acute inflammation. The results showed that a local treatment with 2 mg/ear of alcoholic extract significantly decreased ear edema (65%), while the aqueous extract exerted a weaker inhibitory effect (51%). The anti-inflammatory activity of lentisk was otherwise examined by measuring the secretion of interleukin-1β by macrophages exposed to ATP or H_2O_2. The leaf extract (100 µg/mL) showed significant anti-inflammatory activity compared to acetylsalicylic acid (ASA) [32].

The mechanism of action of indomethacin on inflammation is based on the inhibition of pro-inflammatory prostaglandin synthesis [40]. The anti-inflammatory effect of the acetone extract of *P. lentiscus* fruit is probably attributed to the lipophilic soluble substances that are able to penetrate through the skin barrier [41] and can thereby exert their anti-inflammatory effects. Likely candidates for these anti-inflammatory substances are flavonoids and polyphenols, which have been isolated from *P. lentiscus*. Phenolic compounds are known to interact with and penetrate through lipid bilayers [42]. The observed anti-inflammatory effect is also likely due to the presence of antioxidant compounds in the extract.

The anti-inflammatory results [8][30][31][32][33] provide valuable evidence regarding the anti-inflammatory potential of *P. lentiscus* leaves, suggesting that this plant can be exploited as a natural source of anti-inflammatory agents.

The results obtained in all the studies illustrated above indicate that the extracts of *P. lentiscus* present antioxidant, anti-inflammatory, anticancer, and antimicrobial properties in agreement with the traditional uses of the plant.

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