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Research Article

Ethnobotanical survey, antioxidant activity of *Pistacia lentiscus* leaf extract from Honaïne region (Tlemcen, North-West Algeria) using *in vitro* and *in silico* methods

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Abstract
In recent decades, the study of traditional use of medicinal and aromatic plants has gained in importance. Among these plants, *Pistacia lentiscus*, a traditional medicinal species widespread in Algeria, belongs to the Anacardiaceae family and is characterized by its persistent leaves. It is known locally as "Darw" and is recognized for its several therapeutic virtues since antiquity. This study aimed to gain an understanding traditional use of *P. lentiscus* by the local population of the Honaïne region, through ethnobotanical surveys, antioxidant capacity evaluation using the DPPH (2,2-diphenyl-1-picryl-hydrazyl) free radical scavenging method and docking simulation to predict and evaluate the effectiveness of ligand in binding to the active sites of the receptor glutathione (3R3E). The work showed that this medicinal plant was the most used species in this area, particularly for its therapeutic properties in treating respiratory problems (20%), rheumatism (16%), stomach and intestinal inflammation (14%), and dermatological affections (12%). Its leaves were the most widely used part of the plant (40%), with decoction being the main mode of preparation (35%). The spectrophotometric analyses revealed that this organ had a high total phenolic compounds content (80 mg GAE/g DW) and exhibited satisfactory antioxidant activity (IC_{50}: 0.37 mg/ml), confirming its traditional uses. The molecular docking simulations identified 3,4,5-tri-O-galloylquinic acid as a promising compound with a high docking score against the glutathione 3R3E enzyme (-8.24 kcal/mol). This study highlights the potential for promoting the production of natural antioxidants from *P. lentiscus* as a replacement for synthetic products and the contribution to the knowledge of medicinal flora in Algeria.

Keywords: Algeria, Antioxidant capacity, docking, ethnobotany, *Pistacia lentiscus*

INTRODUCTION

The flora of North Africa results from a multitude of ecosystems, offering a floristic wealth of plant species, several years of which are renowned for their traditional use in human therapy (Quezel and Santa, 1962; 1963; Zitouni, 2017; Chabha, 2024) and because of its climate (Mediterranean, arid and semi-arid) and the nature of its soils, Algeria has a particularly rich flora of medicinal and aromatic plants, most of which grow wild

(Quezel and Santa, 1962; 1963; Felidj*et al.,* 2010; Chabha, 2024). Since ancient times, these plants have formed the basis of popular medicine and can also be used for food or as a condiment. Plant is rarely used whole. More often than not, one or more its parts are involved, each of which may have different applications. Despite advances in pharmacology, the medicinal plants are still widely used for therapeutic purposes in many countries worldwide, particularly in developing countries (Tabuti *et al.,* 2003). Around 4,000 species and subspecies of vascular plants have been inventoried in Algeria; however, less information is known about the country's medicinal flora, with only 146 plant species listed as medicinal (Quezel and Santa, 1962; 1963; Hamel *et al*., 2018). In recent decades, the study of medicinal plants and their traditional use have experienced renewed interest in solving health problems; they constitute an important element of cultural heritage, also due to limited financial resources (El Yahyaoui *et al.*, 2015). In Algeria, the study of traditional medicine is therefore interesting. Among Algerian medicinal and aromatic plants, there is the genus *Pistacia*, which is represented by four species: *Pistacia lentiscus, Pistacia terebinthus, Pistacia vera, and Pistacia atlantica*. *Pistacia lentiscus* L. (pistachio lentisk, *Anacardiaceae*) is a shrub found throughout the mediterranean region. It occupies all altitudes between 0 and 1200 m. This species grows on various soil types such as sandy-clayey-loamy, clayey-loamy, sandy, and clayey soils (Chabha, 2024). The Honaïne area (Tlemcen, North-West Algeria) was the subject of present work, with the objective of contributing to present knowledge, backup the medicinal plants of this region, by conducting ethnobotanical surveys, which focused the present research on the study of pistachio lentisk, plant most prominent within this zone where it with stands soil and climatic stresses perfectly, which it is distinguished from other pistachio trees by its evergreen foliage; the compound leaves are paripinnate, ending in a pair of leaflets, while those of other pistachio trees end in a single leaflet (Benhammou and Atik-Bekkara*,* 2009). The therapeutic properties of this species are part of traditional medicine in several Mediterranean regions, with various applications (Zitouni, 2017). In a second-hand study, we have dosed the phenolic compounds and evaluated the antioxidant activity of their leaf extracts, using spectrophotometric analysis and molecular docking, which evolved as a low-cost and time-saving method for predicting a compound's binding to its target protein. This approach determines crucial properties, such as the active site, angle, location, and binding strength of the compound-protein complex. This discipline enables researchers to gain a deeper understanding of compound-target protein interactions, leading to the development of more effective and targeted therapies (Belhachemi *et al.,* 2022). The research work realized therefore made it possible to establish the link between the use of *P.lentiscus* by the inhabitants of this region and its biochemical value.

MATERIALS AND METHODS

Ethnobotanical study

Study area

The present study was conducted in the Honaïne area in 2023, located approximately 60 km North of the Tlemcen Wilaya in Northwestern Algeria. The region is situated at coordinates 35°10'35"N, 1°39'18"W, or roughly 35.1765° latitude and -1.65503° longitude. The climate in this region is characterized as dry and cold semi-arid.

Methodology

Due to the vast expanse of the research area, efforts were made to pinpoint the most frequently utilized medicinal plants among the local community. Field identification of these species was conducted with reference to the flora of Quezel and Santa (1962, 1963). The inquests of the ethnobotanical investigation were conducted in the form of discussions on the parts used; the method of preparation; the diseases treated and performed using 80 questionnaire forms (Supplementary S1), among people in contact with medicinal plants (villagers, practitioners of traditional medicine and herbalists). The 80 respondents were of both sexes, and of varying intellectual levels.

Dosage of phenolic compounds and antioxidant activity

Plant material

The treated plant material was *Pistacia lentiscus* L. (mastic tree, Fig. 1) leaf, harvested in the Honaïne region, dried at room temperature in the shade, ground to a fine powder, and packaged in a tinted bottle to prevent oxidation of the phenolic compounds, which was then used directly for the extraction of bioactive compounds.

Preparation of leaf extract

The extract was obtained using the method of Djeridane *et al.* (2006, modified); mixture of 20g of leaf powder with 100mL of methanol (80%, from Sigma. This solvent is known not only for obtaining better yields of bioactive compounds but also for its important role in preventing oxidation and degradation of these products) was submitted to continuous agitation for 24 hours at room temperature. The suspension obtained was then filtered by repeating the same operation three times and the filtrates recovered were then evaporated in a rotavaporator (at a temperature of 40°C), then taken up in methanol (80%, adjusted at 25 mg/mL, in a tinted bottle) and stored at 4°C until use.

Fig. 1. *Pistachio lentisk* (*Pistacia lentiscus, Anacardiaceae*)*: Leaves, fruits (berries) and branches*

Determination of total phenolic compounds

The total phenolic compounds in the methanolic extracts were determined spectrophotometrically (6715UV/Vis, Jenway, Multi-cell changer) using the method described by Singleton *et al.* (1999). To 20 µL of extract, 100 µL of freshly prepared Folin-Ciocalteu reagent (0.1 N, Sigma) was added. The mixture obtained was kept at rest for 3 min, then 300µL of a sodium carbonate solution (Na2Co3, 7.5%) was added, adjusted to a final volume of 3mL (by adding distilled water) and left to stand for 90min at room temperature and in the dark to avoid oxidation of the phenolic compounds. In addition, a calibration range for gallic acid (Sigma-Aldrich, Germany) was prepared under the same conditions to determine the content of these bioactive compounds. The reading was taken at an absorbance wavelength of 765 nm. The operation was repeated three times. The results were expressed as milligram equivalent of gallic acid per gram of dry weight (mg GAE/g DW).

2,2-diphenyl-1-picryl-hydrazyl (DPPH) free radical scavenging

To estimate the antioxidant activity of *P. lentiscus* leaves, dilutions were made from methanolic extracts (from 0.02 to 25 mg/mL), following the Brand-Williams *et al.* (1995) protocol, which is as follows: 0.1 mL of each dilution was added to 3.9 mL of freshly prepared DPPH• (2,2-diphenyl-1-picryl-hydrazyl, Sigma, $6X10^{-5}$M). The solutions obtained were then incubated at room temperature for 30min in the dark. Finally, their absorbance was measured at 517 nm. The reference used was ascorbic acid (from Prolabo).

The inhibition percentage (PI%) was calculated using the formula below:

$$PI= (A_0 – A_1) \times 100/A_0 \qquad \text{Eq. 1}$$

Where:

A_0: Absorbance of control

A_1: Absorbance sample (extract with DPPH•)

The findings were expressed as IC_{50}% (the concentration of antioxidant required to decrease the initial concentration by 50%).

Three replicates were performed for the antioxidant assays

Molecular docking

The primary goal of this scientific study was to use molecular docking simulations to predict and evaluate the effectiveness of ligand in binding to the active sites of the crystal structure of the receptor glutathione (3R3E), obtained from the Protein Data Bank (PDB: http://www.rcsb.org/pdb).

Glutathione (3R3E) was chosen as a target protein because it plays an important role in detoxification and protection against oxidative stress. *P. lentiscus*, known for its antioxidant, anticancer and anti-inflammatory effects. This choice enabled us to investigate the interaction of *P. lentiscus*'s bioactive compounds with this protein, thereby improving our understanding of the molecular mechanisms underlying its therapeutic effects against traditional pathologies.

All hydrogen atoms and additional kollman charges were added to the glutathione structure, and non-polar hydrogen atoms were combined. The ligands utilized are obtained from the PubChem database. The docking results were obtained using Autodock 4.2, the graphical user interface program Autodock Tools, and analyzed using Maestro Visualizer.

The inhibitor constant (Ki) was estimated using the equation $Ki=\exp(\Delta G/RT)$, where ΔG, R, and T are the docking energy, gas constant (1.9872036×10^{-3} kcal/mol) and ambient temperature (298.15 K), respectively (Yung-Chi and Prusoff, 1973).

The validation for the docking methodology was performed by re-docking, using RMSD, which provides a good measure of the match between their atomic positions on an atom-by-atom basis. A docking algorithm reproduces a crystallographic conformation if its calculated RMSD is below 2.0 Å.

Statistical analysis

The data were presented as the mean value ± standard deviation. The statistical tests for this study were performed using ANOVA.

RESULTS AND DISCUSSION

Ethnobotanical surveys

Inventory of major medicinal plants

The ethnobotanical study of medicinal plants in the Honaïne region allowed us to compile an inventory of 43 predominantly species encountered and used by the local population with medicinal properties, which are listed in alphabetical order (Table 1).

The botanical identification revealed that the most prevalent families encountered were the *Lamiaceae* (15.55%), followed by the *Fabaceae* and *Cupres-*

Table 1. Ethnobotanical surveys results of medicinal species most commonly used in the Honaïne region (Source: On the basis of the responses of the inhabitants of the population to the questions asked in the form of a survey)

	Latin plant name	Botanical family	Part used	Method of preparation	Disease treated (treatment with each species)
1	*Arenaria serpyllifolia*	*Caryophyllaceae*	Whole plant	Infusion, decoction	Urinary pain (kidney problem)
2	*Arisarum vulgare*	*Araceae*	Leaves, bulbs or tubers	Decoction	Rheumatism, digestive disorders (laxative), headaches, asthma, flu, snake bites, wounds
3	*Artemisia campestris*	*Asteraceae*	Leaves, flowers	Infusion	Muscle spasms, stomach pains (aids gastric digestion), urinary affections (diuretic action) and other affections
4	*Arundo donax*	*Poaceae*	Roots, leaves	Infusion, decoction	Fever, bronchitis, urinary affection, high blood pressure, toxins (depurative action), milk secretion
5	*Brunella grandiflora*	*Lamiaceae*	Leaves, flowers	Infusion, decoction	Bleeding hemorrhoids or minimal bleeding from a wound
6	*Calicotome villosa*	*Fabaceae*	Flowers	Infusion	Affections
7	*Ceratonia siliqua*	*Fabaceae*	Fruit (pods and seeds)	Consumed, decoction, other	Diabetes, digestive disorders (antidiuretic, laxative)
8	*Cistus albidus*	*Cistaceae*	Leaves, branches	Infusion, decoction, fumigation	Rheumatism, coughs, urinary infections, wrinkles
9	*Cistus ladaniferus*	*Cistaceae*	Flowers, leaves, stems	Essential oil	Skin affections (healing and regenerating action), hemorrhage
10	*Cistus monspeliensis*	*Cistaceae*	Flowers	Powder	Skin infections, hemorrhage
11	*Cupressus arizonica*	*Cupressaceae*	Fruits, leaves	Decoction	Rheumatism, respiratory affections
12	*Cupressus sempervirens*	*Cupressaceae*	Fruits	Decoction	Rheumatism, varicose veins, respiratory affections
13	*Echium vulgare*	*Boraginaceae*	Leaves, flowers, roots	Infusion, decoction	Stomach pain, digestive problems
14	*Elymus repens*	*Poaceae*	Rhizome	Powder	urinary affections
15	*Erica multiflora*	*Ericaceae*	Leaves, flowers	Infusion, decoction	Urinary infection
16	*Genista anglica*	*Fabaceae*	Stems, flowers, leaves	Infusion	Heart problems, urinary infections, toxins
17	*Genista pilosa*	*Fabaceae*	Flowers, stems, leaves	Infusion	Heart problems, toxins
18	*Genista scorpius*	*Fabaceae*	Flowers, stems, leaves	Infusion	Heart problems, urinary infections, toxins, high blood pressure, rheumatism
19	*Inula viscosa*	*Asteraceae*	Leaves, stems	Decoction	Respiratory diseases, rheumatism, urinary diseases, digestive disorders
20	*Jasminum fruticans*	*Oleaceae*	Flowers	Infusion	Digestive problems, insomnia
21	*Juniperus oxycedrus*	*Cupressaceae*	Leaves, fruits	Infusion	Rheumatism, digestive disorders, other affections
22	*Juniperus phoenicea*	*Cupressaceae*	Leaves, fruits	Infusion	Rheumatism, urinary infections, other affections
23	*Lavandula dentata*	*Lamiaceae*	Flowers, leaves	Infusion, fumigation	Rheumatism, urinary disorders, toxins, other affections, headaches

Contd…….

Table 1. Contd….

24	Lavandula stoechas	*Lamiaceae*	Flowers, leaves	Infusion	Respiratory affections
25	*Malva sylvestris*	*Malvaceae*	Flowers, stems	Infusion, consumed	Respiratory affections (cough, throat irritation, asthma), intestinal disorders (constipation)
26	*Myrtus communis*	*Myrtaceae*	Leaves, flowers, fruits	Infusion	Respiratory affections, diarrhea, hemorrhoids
27	*Opuntia ficus-indica*	*Cactaceae*	Flowers, fruits, stems	Consumed, infusion	Urinary affections, wrinkles, fatigue
28	*Picea pungens*	*Pinaceae*	Needles	Infusion	Respiratory affections
29	*Pinus halepensis*	*Pinaceae*	Seeds, bark	Infusion, decoction	Cholesterol, respiratory affections (colds, bronchitis)
30	*Pistacia lentiscus*	*Anacardiaceae*	Whole plant	Decoction,infusion, powder, fixed oil, essential oil	Respiratory, stomach,dermatological affections and Rheumatism
31	*Plantago media*	*Plantaginaceae*	Leaves	Infusion, decoction	Respiratory affections, burns
32	*Platanus occidentalis*	*Platanaceae*	Leaves, roots	Decoction	High blood pressure
33	*Rosmarinus officinalis*	*Lamiaceae*	Leaves, flowers, stems	Infusion, decoction, fumigation	Rheumatism, stress, respiratory affections, stomach pains, burns, healing, dyspepsia (stomach pains linked to poor digestion: Carminative).
34	*Rubus caesius*	*Rosaceae*	Leaves, fruits	Infusion, consumed	Respiratory affections
35	*Satureja montana*	*Lamiaceae*	Leaves	Infusion, decoction	Affections
36	*Silene latifolia*	*Caryophyllaceae*	Roots	Decoction	Respiratory and urinary affections
37	*Sinapis arvensis*	*Brassicaceae*	Leaves, stems, flowers	Consumed	Fatigue
38	*Tamarix aphylla*	*Tamaricaceae*	Pulp, bark, leaves	Infusion, decoction, maceration	Respiratory affections, digestive problems (laxative), anaemia
39	*Tetraclinis articulata*	*Cupressaceae*	Leaves, stems	Infusion, decoction	Rheumatism, respiratory affections (coughs, colds)
40	*Thymus capitatus*	*Lamiaceae*	Aerial part	Infusion	Affections
41	*Thymus vulgaris*	*Lamiaceae*	Aerial part	Infusion, fumigation	Affections
42	*Trifolium thalii*	*Fabaceae*	Leaves, flowers	Infusion	Respiratory affections
43	*Urtica dioica*	*Urticaceae*	Leaves, roots	Infusion	Urinary affections, anemia

saceae, with 13.33% and 11.11%, respectively. In the Tlemcen Mountains national park, Felidj et al. (2010) recorded that Asteraceae predominated (18%), followed by Poaceae (8%), Fabaceae, and *Lamiaceae* (7%). According to these authors, the mountains of Tlemcen as a whole offer highly diverse botanical landscapes linked to the various climatic, soil, and topographical conditions specific to the region, which stretches from the coast to the high plateaus of the Tellian Atlas. For thousands of years, the region's forest heritage has undergone changes due to climatic variations and human activity (deforestation, overgrazing), the latter reinforced by more recent climatic variations (summer drought, irregular rainfall). Several species classified as endemic are in the process of regression or even extinction due to the degradation of their natural environment. Among the most well-known in terms of regression: *Delphinium mauritanicum, Genista tricuspidata, Hippocrepis minor ssp mumbyana, Scrofularia laevigata, Thymus ciliates ssp coloratus, Centaurea parviflora, Helianthemum helianthemoïdes, Thymus algeriensis.* These authors also reported that one of the endemic species most threatened by the current rapid and intensive degradation of the environment is *Ammoides pussila* (an aromatic and medicinal plant).

According to several studies carried out in Algeria and Morocco (Salhi *et al.,* 2010; El Hilah *et al.,* 2015; El Alami *et al.,* 2016; Khitri *et al.,* 2016; Rhattas *et al.,*2016;

Kadri *et al.,* 2018; Mansouri *et al.,* 2018; Lazli *et al.,* 2019), the most frequently found botanical families are as follows: *Lamiaceae, Poaceae, Apiaceae, Astéraceae, Fabaceae, Solanaceae, Caryophylaceae, Brassicaceae, Cistaaceae, Ranunculaceae, Rubiaceae, Plantaginaceae, Apocynaceae, Thymelaeaceae, Cupressaceae, Pinaceae, Myrtaceae, Malvaceae, liliaceae, Asparagaceae, Ericaceae and Anacardiaceae*.

The present analysis also revealed that women used medicinal plants more frequently (62.50%) than men (37.50%), a finding that has been reported by several authors (Hmamouchi, 2001; Salhi *et al.,* 2010). Indeed, the vast majority of medicinal plants users are much more old people.

Usage of *Pistacia lentiscus* by the local population

In the region studied, the species most commonly used by the inhabitants was the *Pistachio lentisk* (*Pistacia lentiscus*, 20%: Anacardiaceae), known in Algeria as "Darw". The results obtained from ethnobotanical surveys will be deposited in the reference herbarium at the National Higher School of Agronomy in Algiers. These findings align with those of Souilah *et al.* (2023) in the El Kala zone (northeastern Algeria), where its usage was estimated at 9.69%.

In Honaïne,The leaves were the most widely used part of the plant, accounting for 40% (Table 2). According to the ethnobotanical study of the *P. mastic* tree carried out in the Wilaya of El Tarf, North-East Algeria (Beldi *et al.*, 2021), the fruits with oil were the most commonly used parts of this plant (66% vs. 24% for the leaves). Regarding the method of preparation, decoction was recorded first, with a percentage of 35, and the disease most treated in the region studied by *P. lentiscus* was respiratory affections (20%). In eastern Algeria, in addition to external applications, the fixed mastic oil extracted is also used to treat respiratory problems (Belhachat, 2019), in comparison with the leaves, stems, and roots, which are rather recommended for internal applications.

Generally, the high frequency of leaf use has already been reported in other studies of medicinal plants, such as those by Benlamdini *et al.* (2014), Rhattas *et al.* (2016), Kadri *et al.* (2018), and Lazli *et al.* (2019). This can be explained by the ease and speed of harvesting, but also by the fact that they are the site of photosynthesis and the storage of secondary metabolites (biological activities) (Bitsindou,1986; Salhi *et al.,* 2010).

In other areas of Algeria and Morocco, the researchers listed above reported that aqueous decoction, infusion and powder were the most commonly used preparation methods. Salhi *et al.* (2010) explain this by saying that decoction allows the most active ingredients to be collected and reduces or cancels out the toxicity of certain medicinal plants recipes. Indeed, in phytotherapy, there are various ways of preparing plants, depending on the type of application (El Hilah *et al.,* 2015). Generally, infusion is suitable for the fragile parts of plants (flowers, leaves, parts rich in volatile and aromatic substances), while decoction is the preferred method for the more rigid and fibrous parts of the plant (certain roots, leaves, seeds, and bark). Other preparation methods, such as maceration (cold infusion) are generally used for plants containing thermolabile and heat-sensitive compounds (such as plants rich in mucilage). Kadri *et al.* (2018) noted that medicinal plants were used to treat respiratory diseases. However, the other authors mentioned above have observed that the majority of these plants are used to care for the digestive system, while others are used to treat a variety of ailments.

Total phenolic compounds determination

A content of 80±0.6 mg GAE/g DW of total phenolic compounds was estimated in pistachio lentisk leaves. Comparing this findings level obtained with those of the studies carried out by Zitouni (2017), Lasmar and Laribi (2020) and Souilah *et al.* (2023), a difference is noticed; they were higher than those of the present work, these authors registered a content of 216 (in leaves of the same species, from the Nédroma region, Tlemcen), 155 (in leaves from the Skikda area) and 306.5 mg GAE/gDW (in El-Kala area, Algeria), respectively, which of the leaf was the part of the plant richest in these bioactive compounds, compared with the rest of the organs (fruit, seeds, root and stem). In contrast, the levels obtained in the leaves of Ain Fezza (Tlemcen) were lower: 0.90 mg/g of dry extract (Benhammou *et al.,* 2007).

This difference in results can be attributed to the variations in climatic and soil conditions of the plant's biotope and interspecific differences (Arab *et al.,* 2014), as well as the harvesting stage of pistachio lentisk leaves. It may also be due to extraction conditions (Benhammou and Atik-Bekkara*,* 2009; Chu *et al.,* 2022), in particular the method used and the presence of interfering substances (Gouegoui Bohui *et al.,* 2018). Furthermore, the fixed oil extracted from the fruits of this plant species (in the Jijel region, Algeria) contained a content of 1.264 mg GAE/g oil (Sid and Dib, 2018).

***In vitro* antioxidant activity**

The antioxidant activity determined using the DPPH• free radical scavenging method. revealed that the leaf extract of *P. lentiscus* has a satisfactory antioxidant power (with an IC_{50} approximate value of 0.37±0.09 mg/mL (370 µg/mL) of extract, Fig. 2), which supports the traditional use of this part of the plant by the Honaïne population (traditional medicine): The leaves are used especially to treat respiratory problems and asthma, eczema and stomach pains, for example, a decoc-

Table 2. Ethnobotanical study of *Pistacia lentiscus* (Source: Based on the responses of the inhabitants of the population to the questions asked in the form of a survey)

Plant name	**Part used percentage**	**Preparation method (mode for each organ)**	**Preparation percentage**	**Percentage of Disease treated**
Pistacia lentiscus	Leaves (40%)	Decoction, infusion and powder	Decoction (35%) Infusion (25%) Powder (20%) Fixed oil (18%) Others (2%)	Respiratory allergy problems, bronchitis, asthma (20%: By using leaf and stem) Rheumatism (16%: By using roots) Colon and stomach inflammation (14%: By using leaf, stem and roots), Eczema, burns (12%: By using leaf, stem and fixed oil) Others ailments (38%)
	Branches (25 %)	Decoction, infusion		
	Roots (20%)	Decoction		
	Fruit (15%)	Fixed oil traditionally extracted cold		

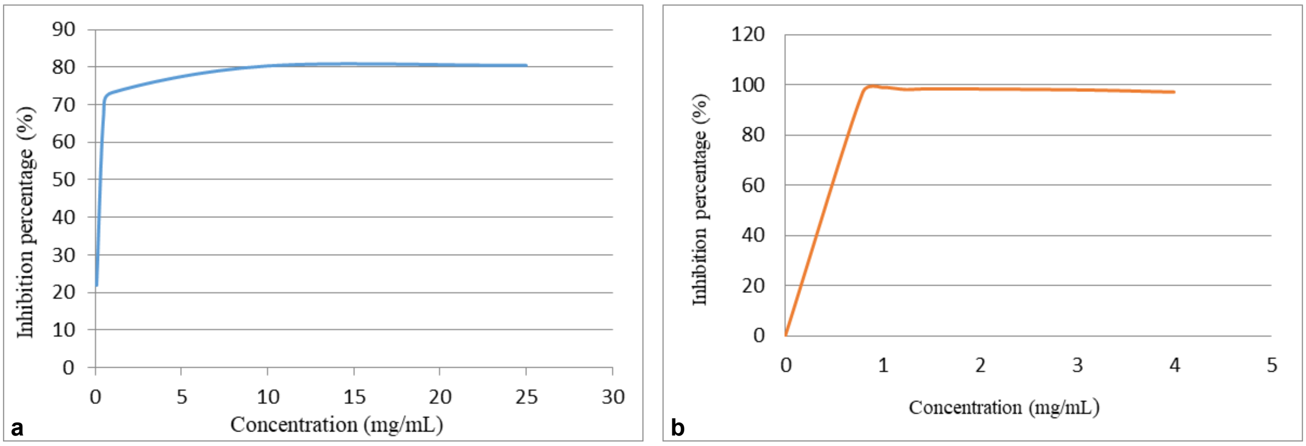

Fig. 2. *In vitro anti-radical activity. a, Profile of Pistacia lentiscus leaf extract; b, Profile of ascorbic acid*

tion of the dried roots is effective against ulcers and intestinal inflammation. In fact, *P. lentiscus* is a medicinal plant used to treat a range of diseases, including rheumatism, by promoting lymphatic and venous drainage (Belhachat, 2019). On the other hand, Beldi*et al.* (2021) reported that when applied externally, the leaves and stems are recommended for the treatment of skin problems. These parts of the plant are then dried and ground to obtain a powder to which vegetable oil or butter will be added. For internal use, the leaves and stems can also be used as an infusion to treat conditions of the digestive and respiratory systems, as well as dizziness. According to Simić *et al.* (2007), phenolic compounds can function as antioxidants due to their ability to capture free radicals, there by interrupting the chain of free radicals through their hydrogen-donating effect. We can therefore explain the foliar antioxidant potential of *P. lentiscus* obtained by its phenolic composition.

As follows to Baratto *et al.* (2003), the free radical scavenging activity in the leaves of the *P. lentiscus* increases with the number of galloyl groups on the quinic acid backbone (galloyl quinic derivatives). According to Zitouni (2017), who worked on the same species, hydroxycinnamic acids have been shown in numerous studies to be the most potent phenolic compounds, exhibiting antioxidant, anticancer, and anti-inflammatory effects. According to this author, five hydroxycinnamic acids have been identified in *P. lentiscus* (caffeic acid, ferulic acid, synapic acid, rosmarinic acid, ρ-coumaric acid) and others seventeen phenolic compounds (including luteolin, luteolin 7-O glucoside, isoquercitrin, hyperoside, oleuropein, rutin, kaempferol, kaempferol 3-O rutinoside, isorhamnetin, apigenin, laricitrin and polydatin of which twelve flavonoids have been identified). It is well known that flavonoids offer a wide range of biological properties, including anti-inflammatory and antioxidant activities, which make them potentially useful in the prevention of cancer, diabetes and neurodegenerative diseases (Kang *et al.*, 2010; Zitouni, 2017; Emeraux, 2019).

Moreover, the present work results are close to those of the study by Arab *et al.* (2014, IC_{50}: 0.2 mg/mL, for leaves from the Boumerdes region). These authors demonstrated that the phenolic extract proved very good antioxidant activity compared to other parts of the plant. Additionally, Belhachat *et al.* (2017) and Belhachat (2019) declared that the extracts of the leaves, red fruits, and black fruits of *P. lentiscus* (Bouira area) were more effective than the essential oils (IC_{50} of

0.758, 0.870, and 0.880 mg/L, respectively). In addition, the IC_{50} value obtained is comparable to that reported by Zitouni (2017), which found the most potent anti-radical activity in the leaf and stem parts with IC_{50} values of 0.069 and 0.057 mg/mL, respectively. On the other hand, compared to other literature, the results obtained are negligible in comparison to those of Lasmar and Laribi (2020), who reported a fairly high potency in the species studied from the Skikda area (IC_{50}: 1.4 µg/mL). Souilah *et al.* (2023) have registered an IC_{50} of 2.75 µg/mL. This can be attributed to the chemical composition of the plant studied, which varies according to factors such as geographical origin, harvesting period, environmental conditions, and storage time (Su *et al.,* 2006).

Indeed, all therapeutic properties of *P. lentiscus* are due to its biological activities (antimicrobial, antioxidant, anti-inflammatory, anti-hypertensive and insecticide, Benhammou *et al.,* 2007; Benhammou and Atik-Bekkara, 2009; Belhachat, 2019; Lasmar and Laribi, 2020).

Molecular docking

It has recently emerged as an effective method for *in silico* screening. It includes a computer search for ligands that are both energetically and geometrically compatible with a protein's binding site (receptor).

A molecular docking study was conducted on three phenolic compounds of *P. lentiscus: 3,4,5-tri-O-galloylquinic acid,* ρ-coumaric acid and caffeic acid, to investigate their mode of inhibition in the binding site of glutathione (3R3E). The docked compounds exhibited strong binding affinities against the active site of glutathione (3R3E), and their ligand-receptor interactions were illustrated using 2D and 3D diagrams (Fig. 3), revealing the predominant formation of hydrogen bonds with residues in the active site and electrostatic interactions.

Specifically, 3,4,5-tri-O-galloylquinic acid interacted with the active site by forming four hydrogen bonds with Ser149, Glu148, Asn147 and Tyr187 amino acids, as well as electrostatic interactions such as van der Waals interactions with Trp65 and Arg130 (Fig.3e, f). The interaction between ρ-coumaric acid and the active site involved three hydrogen bonds with Ser149, Asn147, and Tyr187 amino acids, along with electrostatic interactions including van der Waals interactions with Trp65 (Fig.3c,d). Likewise, the interaction between caffeic acid and the active site was characterized by four hydrogen bonds with the amino acids Glu148 (1 bond), Ser149 (2 bonds), and Val133 (1 bond), as well as electrostatic interactions, including van der Waals interactions with Trp65 (Fig. 3a, b).

Table 3 summarises the data from the binding energies and Ki of 3,4,5-tri-O-galloylquinic acid, ρ-coumaric acid and caffeic acid. The binding energies between the three chemicals and the protein 3R3E predicted to be -8.24 kcal/mol, -6.10 kcal/mol and -5.94 kcal/mol, respectively. Redocking was successfully performed with RMSD of 1.3845 (<2Å).

The binding energy and Ki results showed that the complex formed by 3,4,5-tri-O-galloylquinic acid and the target protein exhibited the best binding interactions, indicating good and strong stability compared to the other two complexes formed by ρ-coumaric acid and caffeic acid with the protein. The Ki for ρ-coumaric acid-3R3E and caffeic acid-3R3E complexes is 33.78 µM and 44.25 µM, respectively. The hydrophobic interaction with the residual amino acids in the glutathione activation site and the hydrogen bonding interaction with the amino acid in the activation site of the compounds studied make them promising candidates for glutathione 3R3E.

Molecular docking study by Lanez *et al.* (2022) showed that 3-nitrophenylferrocene is the most inactive compound against glutathione reductase enzyme, having the lowest docking score of -16.96 kJ/mol. Bouaklineet *al.* (2024) confirmed that the finding of anti-diabetic activity was consistent with the molecular docking study of the main phenolic compounds of *P. lentiscus* leaf extracts, where a remarkable binding affnity against *α*-amylase was observed, with values of −7.631 (kcal/mol), −6.818 (kcal/ mol), and −5.517 (kcal/ mol) for the major compounds catechin, quercetin-3-

Table 3. Docking scores of ligand with glutathione 3R3E

Compound	Binding scores (kcal/mol)	Type of bond	Ki (µM)
Caffeic acid	-5.94	Conventional Hydrogen Bond Pi-Pi Stacked Pi-Alkyl	44.25
ρ-coumaric acid	-6.10	Conventional Hydrogen Bond	33.78
3,4,5-tri-O-galloylquinic acid	-8.24	Conventional Hydrogen Bond Pi-Pi Stacked Pi-Alkyl	0.9

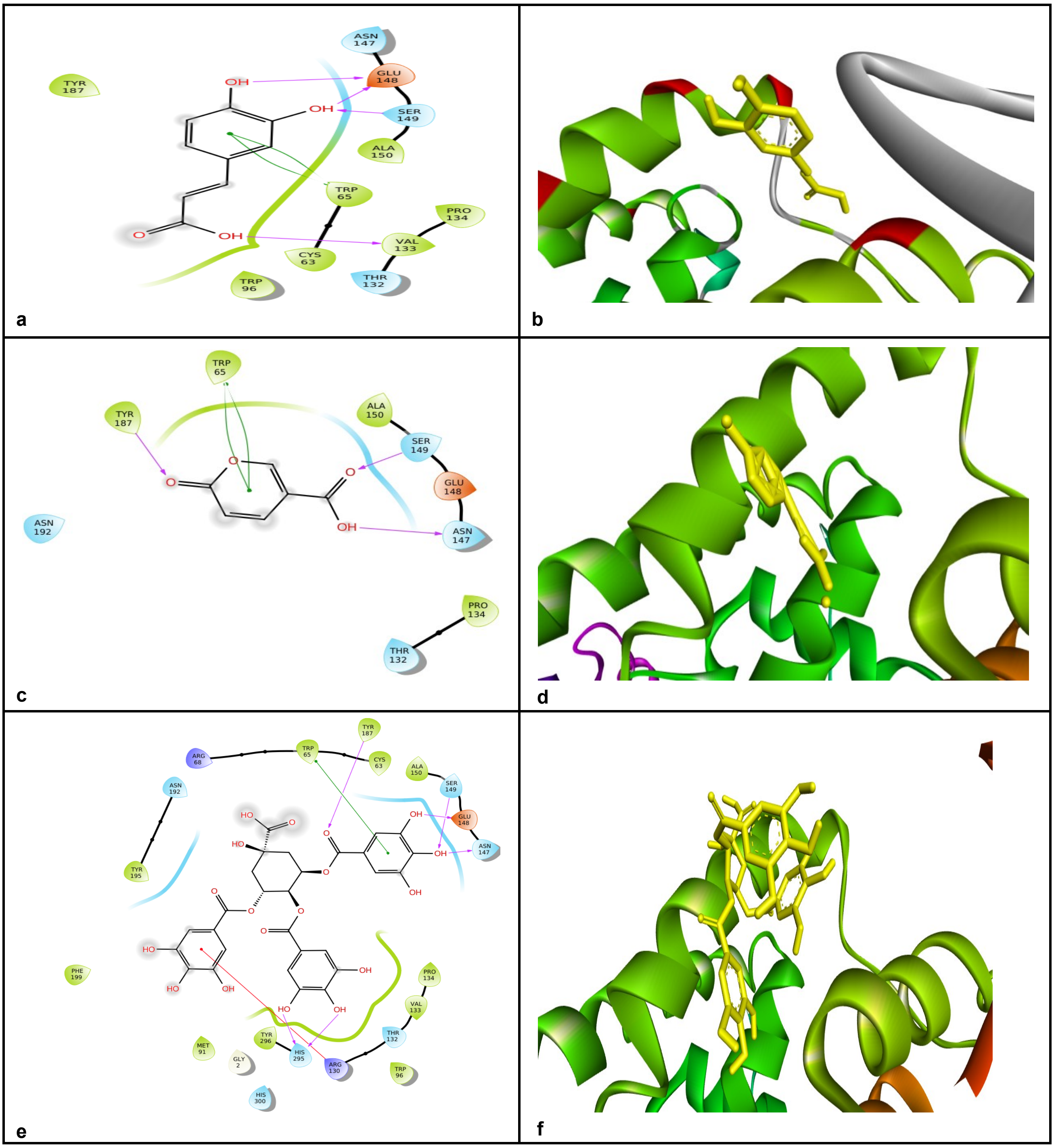

Fig. 3. *Interactions of caffeic acid, ρ-coumaric acid and 3,4,5-tri-O-galloylquinic acid within glutathione binding site (PDB: 3R3E). 2D (a) and 3D (b) interactions of caffeic acid; 2D (c) and 3D (d) interactions of ρ-coumaric acid; 2D (e) and 3D (f) interactions of 3,4,5-tri-O-galloylquinic acid*

glucoside, and gallic acid, respectively.

Conclusion

The present study focused on an ethnobotanical survey from the Honaine region of Algeria, concentrating on *P. lentiscus* and its most important uses. This work was complemented by an estimation of phenolic compound content, molecular docking and antioxidant activity of its leaf extracts, which is commonly used in the study area, to establish a link between the use of this medicinal plant and its biochemical properties. The results obtained a significant amount of phenolic compounds and a satisfactory antioxidant power, which could constitute a database for further research on this organ. This could be used as an active ingredient in anticancer drugs or as food additives to replace synthetic compounds. However, this work needs to be followed up by other studies; for example, it would be more interesting to conduct chromatographic analyses to identify the active principles of this plant. It would also be important to conduct experimental research to estimate the biological activities of others (antimicrobial, anti-inflammatory, antidiabetic, anticancer activities) in *P. lentiscus* and the other medicinal plants identified in this work, to gain a better understanding of them and develop them in pharmacology.

Supplementary Information

The author(s) is responsible for the content or functionality of any supplementary information. Any queries regarding this matter should be directed to the corresponding author. The supplementary information is available for download from the article's webpage and will not be included in the print copy.

Conflict of interest

The authors declare that they have no conflict of interest.

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