

## Review Article

# Five *Pistacia* species (*P. vera*, *P. atlantica*, *P. terebinthus*, *P. khinjuk*, and *P. lentiscus*): A Review of Their Traditional Uses, Phytochemistry, and Pharmacology

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*Pistacia*, a genus of flowering plants from the family Anacardiaceae, contains about twenty species, among them five are more popular including *P. vera*, *P. atlantica*, *P. terebinthus*, *P. khinjuk*, and *P. lentiscus*. Different parts of these species have been used in traditional medicine for various purposes like tonic, aphrodisiac, antiseptic, antihypertensive and management of dental, gastrointestinal, liver, urinary tract, and respiratory tract disorders. Scientific findings also revealed the wide pharmacological activities from various parts of these species, such as antioxidant, antimicrobial, antiviral, anticholinesterase, anti-inflammatory, antinociceptive, antidiabetic, antitumor, antihyperlipidemic, antiatherosclerotic, and hepatoprotective activities and also their beneficial effects in gastrointestinal disorders. Various types of phytochemical constituents like terpenoids, phenolic compounds, fatty acids, and sterols have also been isolated and identified from different parts of *Pistacia* species. The present review summarizes comprehensive information concerning ethnomedicinal uses, phytochemistry, and pharmacological activities of the five mentioned *Pistacia* species.

## 1. Introduction

The genus *Pistacia* belongs to the Anacardiaceae, a cosmopolitan family that comprise about 70 genera and over 600 species. The species of the genus *Pistacia* are evergreen or deciduous resin-bearing shrubs and trees which are characterized as xerophytic trees and growing to 8–10 m tall. *Pistacia lentiscus* L., *P. atlantica* Desf., *P. terebinthus* L., *P. vera* L., and *P. khinjuk* Stocks. are distributed from the Mediterranean basin to central Asia [1, 2]. Three *Pistacia* species naturally occur in Iran: *P. vera* L., *P. khinjuk* Stocks., and *P. atlantica* Desf.; *P. atlantica* has three subspecies or varieties which have been described as *cabulica*, *kurdica*, and *mutica* [3]. *P. vera* is the only species of the genus cultivated commercially, and the rest of the species are mostly used as rootstocks for *P. vera* [1, 2].

Different parts of *Pistacia* species have been investigated for various pharmacological activities. Most of the papers are devoted to the resin of *P. lentiscus* that is known as mastic. In addition to their therapeutic effects, *Pistacia* species are used in food industry, for example, consumption of pistachio (*P. vera*) nut as food additive [4], *P. terebinthus* fruit as snack food or in making coffee-like drink [5, 6], and the anthocyanin composition of *P. lentiscus* fruit as food colorants [7].

Chemical studies on *Pistacia* genus have led to discovering diverse secondary metabolites in addition to high level of vitamins and minerals.

Our review presents a comprehensive report on phytochemical aspects, pharmacological activities, and toxicity of the genus *Pistacia* by focusing on the data reported since

the year 2000 via papers on databases including PubMed, Scopus, Google Scholar, and Web of Science.

## 2. Traditional Uses

Traditional uses, plant part used, and pharmacological activities of *Pistacia lentiscus*, *P. atlantica*, *P. terebinthus*, *P. vera*, and *P. khinjuk* from different regions are listed in Table 1.

Different parts of *Pistacia* species including resin, leave, fruit, and aerial part have been traditionally used for a wide range of purposes. Among them, *P. lentiscus* is the most commonly used in different regions and resin of that has been utilized for as long as 5000 years. Resin of *P. lentiscus* has been used for variety of gastric ailments in the Mediterranean and Middle East countries for the last 3000 years [8]. It was used in ancient Egypt as incense; it has also been used as a preservative and breath sweetener [4]. Most of the traditional uses reports for resin of *P. atlantica* are from Iran and have been used for the treatment of digestive, hepatic, and kidney diseases [9]. Fruit of *P. vera* (pistachio) is used all over the world. Records of the consumption of pistachio as a food date to 7000 BC [4]. Pistachio is cultivated in the Middle East, United States, and Mediterranean countries. Iran is one of the biggest producers and exporters of pistachio nuts [10]. In traditional Iranian medicine (TIM), different parts of *P. vera*, *P. atlantica*, *P. khinjuk*, *P. terebinthus*, and *P. lentiscus* have been used for a long time as useful remedies for different diseases, for example, the fruit kernel of *P. vera* as a cardiac, stomach, hepatic, and brain tonic; the fruits of *P. atlantica*, *P. khinjuk*, and *P. terebinthus* for their aphrodisiac activity and treatment of liver, kidney, heart, and respiratory system disorders, and the gum resin of *P. lentiscus*, *P. atlantica*, *P. khinjuk*, and *P. terebinthus* for their wound healing activity, and treatment of brain and gastrointestinal disorders [9, 11].

## 3. Phytochemical Studies

Various compounds from different phytochemical groups were identified in *Pistacia* species. These are summarized below and also in Table 2 based on the structure of finding components.

### 3.1. Terpenoids

**3.1.1. Monoterpenoids, Sesquiterpenoids, and Volatile Oil.** Essential oil is one of the main components reported from different parts of *Pistacia* species including leaves, resin, ripe and unripe fruits, galls, leaf-buds, twigs, and flowers. Analysis of essential oils is mostly performed by means of gas- chromatography (GC) based techniques. There are many qualitative and quantitative variations between the content of essential oils. These variations are related to several parameters like plant species and part, sex of cultivars, harvesting time, geographical origin, and climatic conditions [12, 13]. Hydrocarbon and oxygenated monoterpenes are the major chemical constituents in essential oil and among hydrocarbon monoterpenes,  $\alpha$ -pinene (1) has been reported as the main compound of some samples like *P. vera* [12, 14, 15],

*P. terebinthus* [16–18], *P. lentiscus* [19–24], and *P. atlantica* [25–27]. In addition to  $\alpha$ -pinene, other major components isolated from different parts of *Pistacia* species are as follows: limonene (2),  $\alpha$ -terpinolene, and ocimene (3,4) from fruits and leaves of *P. vera* [28]; (*E*)- $\beta$ -Ocimene (5) and limonene in fruits [18, 28, 29]; (*E*)- $\beta$ -Ocimene and terpinen-4-ol (6) in leaves and *p*-cymen, (7) in young shoots of *P. terebinthus* [28–30]; bornyl acetate (8), terpinen-4-ol, sabinene (9), and myrcene (10) in fruits, terpinen-4-ol, myrcene, *p*-mentha-1 (7),8 diene (11), and ocimene from leaves [27, 28, 31], sabinene and *p*-mentha-1 (7),8 diene in leaf buds, and  $\Delta^3$ -carene (12) in unripe galls of *P. atlantica* [31, 32]. Monoterpenes are also detected in mastic water which was separated from the mastic oil during steam distillation. Verbenone (13),  $\alpha$ -terpineol (14), linalool (15), and *trans*-pinocarveol (16) are the main constituents of mastic water [33].  $\beta$ -pinene (17) in oleoresin,  $\beta$ -myrcene and sabinene in fruits [28, 30, 34], terpinen-4-ol in aerial parts [22], and limonene, myrcene, sabinene, and terpinen-4-ol in leaves of *P. lentiscus* were determined as the main composition [28, 30, 35, 36].

Some of the other monoterpenes identified as effective antibacterial components of these essential oils are camphene (18), limonene, and carvacrol (19) from *P. vera* resin [12].

Sesquiterpenes isolated in lower amount compared with monoterpenes. Germacrene-D (20) and  $\beta$ -caryophyllene (21) were identified in *P. lentiscus* and *P. terebinthus* leaves with higher concentration in comparison with other sesquiterpenes [28]. Spathulenol (22), an azulenic sesquiterpene alcohol, is the predominant component of leaves of *P. atlantica* and *P. khinjuk* [37, 38]. Congiu et. al. [34] recovered Caryophyllene with the highest amount from *P. lentiscus* leaves by means of supercritical CO<sub>2</sub> extraction. Germacrene-D in *P. terebinthus* flowers,  $\beta$ -caryophyllene in *P. lentiscus* galls, and Longifolene (23) in aerial parts of *P. lentiscus* are dominant [24, 29, 39].

**3.1.2. Diterpenoids.** Trace amounts of Diterpenoids were isolated from the essential oil of these species. Abietadiene (24) and abietatriene (25) were detected in essential oil of *P. vera* resin [12].

**3.1.3. Triterpenoids.** Resin of these species has been characterized by penta and tetracyclic triterpenes. Triterpenes such as masticadienonic acid (26), masticadienolic acid (27), morolic acid (28), oleanolic acid (29), ursonic acid (30) and their derivatives have been detected in acidic fractions of *P. lentiscus*, *P. terebinthus*, and *P. atlantica* resins [40–42]. Several triterpenoid compounds were isolated from neutral fraction of *P. lentiscus* and *P. terebinthus* resins like tirucallol (31), dammaradienone (32),  $\beta$ -Amyrin (33), lupeol (34), oleanolic aldehyde, and 28-norolean-12-en-3-one. Quantitative and qualitative varieties in chemical composition of resins according to the method of collection were reported [40, 41].

Anti-inflammatory properties have been reported from masticadienolic acid, masticadienonic acid, and morolic acid isolated from *P. terebinthus* [43]. Among triterpenes isolated from the resin of three sub-species of *P. atlantica* (*kurdica*,

TABLE I: Ethnomedicinal uses of selected *Pistacia* species.

Species	Regions	Plant part(s) used	Traditional uses and ethnobotanical reports	Reference(s)
<i>Pistacia lentiscus</i>	Algeria	Leaf	Appetizer and astringent	[75]
	Greece	Resin	Stomach ache, dyspepsia, stomach ulcer, intestinal disorders, hepatic inflammation, tooth disease, diabetes, hypercholesterolemia, and diuretic	[33, 128, 129]
		Aerial part	Stimulant, diuretic, hypertension, kidney stones, jaundice, cough, sore throat, eczema, and stomach ache	[88]
	Iraq	Resin	Abdominal pain	[130]
	Iran	Resin	Gum tissue strengthener, breath deodorizer, brain and liver tonic, and gastrointestinal ailments	[11, 100, 102]
	Italy	Leaf	Toothache, mycosis, herpes, abdominal and intestinal pain, rheumatism, antiseptic, cicatrizant, emollient, expectorant, and astringent	[131, 132]
	Jordan	Leaf	Jaundice	[121, 133]
		Resin	Heart burn and stomach ache	
	Morocco	Leaf	Digestive disease, evil eye	[134]
		Leaf, bark	Gastric analgesic	[135]
	Portugal	Root	Antiseptic and antiodontalgic	[135]
		Seeds	Antirheumatic	[135]
		Stem	Buccal antiseptic	[135]
	Spain	Aerial part	Hypertension	[136]
		Fruit	Influenza	[71]
		Leaf	Dermatophytosis in cows	[72]
	Tunisia	Tender bud	Warts	[73]
			Fruit	Edible usage, condiment, scabies, Rheumatism, and antidiarrheal
	Turkey	leaf	Eczema, diarrhea, throat infections, paralysis, kidney stones, Jaundice, asthma, stomach ache, astringent, anti-inflammatory, antipyretic, and stimulant	[96]
<i>Pistacia atlantica</i>	Algeria	Fruit	Stomach ache, cough, stress, tonic, and antidiarrheal	[20, 63]
	Greek	Fruit	Mouth flavouring, tanning, and as fodder	[31]
		Aerial part	Veterinary	[31]
	Iran	Fruit	Antidiarrheal	[11]
		Resin	Peptic ulcer, mouth freshener, antiseptic, gum tissue strengthener, as chewing gum, appetizer, phlegm dissolver, astringent, laxative, demulcent, diuretic, emmenagogue, carminative, visceral inflammation, scabies, stomach, liver and kidneys tonic, gastrointestinal disorders, and motion sickness	[9]
			Resin, bark	Joint pains, toothache, wound healing
	Jordan	Fruit	Stomach ache	[133]
		leaf	Antidiabetic	[109]
	Morocco	Leaf	Eye infection	[134]
		Resin	Gum tissue strengthener, breath deodorizer, cough, chill, and stomach disease	[27]
	Turkey	Fruit	Mouth disease	[138]
		leaf	As vegetables and food	[127]
	Resin	Wound healing	[138]	

TABLE I: Continued.

Species	Regions	Plant part(s) used	Traditional uses and ethnobotanical reports	Reference(s)
<i>Pistacia terebinthus</i>	Greece	Resin	Antidote, aphrodisiac, expectorant, and treatment of leprosy	[139]
	Iran	Resin	Smoke of it as air purifier and antiseptic	[140]
		Leaf, bark	Astringent and antidiarrhea	[11]
	Jordan	Resin	Diuretic, laxative, stimulant, and aphrodisiac	[18]
		Leaf	Diuretic, antihypertensive, and treatment of jaundice	[18]
	Spain	Aerial part	Hypotensive and cephalalgic	[141]
		Branch	Antiseptic	[141]
		Flower, leaf	Odontalgia and Dislocated joint	[142]
		Fruit	Antiprostatitis	[141]
		Fruit	Cold, flu, diuretic, stomach ache, rheumatism, stimulant, antitussive, appetizer, as coffee, urinary inflammations, and soap production	[29, 53, 138, 143]
Turkey	Leaf	Stomach ache, mycosis, and antidiabetic	[29, 53, 144, 145]	
	Resin	Urinary and respiratory antiseptic, asthma, antipyretic, and anti-inflammatory	[53]	
<i>Pistacia vera</i>	Iran	Nut shell	Tonic, sedative, and antidiarrhea	[11]
		Fruit	Food	[10]
	Jordan	Oil	Facial skin cleanser	[133]
	Turkey	Resin	Asthma, stomach ache, and hemorrhoids	[146]
<i>Pistacia khinjuk</i>	Iran	Aerial part	Veterinary use	[147]
		Resin	Stomach discomfort, nausea, vomiting, and motion sickness	[148]

*cabulica* and *mutica*), 3-O-acetyl-3-epiisomasticadienolic acid (**35**) has been identified as the most effective antimicrobial agent [42].

**3.2. Phenolic Compounds.** Gallic acid (**36**), catechin (**37**), epicatechin (**38**), and gallic acid methyl ester were identified in *P. vera* seed and skin, leaves of *P. lentiscus* and leaves and galls of *P. atlantica* [44–46]. Bhourri et al. [47] demonstrated that digallic acid (**39**) from fruits of *P. lentiscus* has antimutagenic properties. Monounsaturated, diunsaturated, and saturated cardanols have been detected in *P. vera* kernel. 3-(8-Pentadecenyl)-phenol (**40**) was the dominating cardanol in *P. vera* [48]. Trans and cis isomers of phytoalexin, resveratrol (3,5,4'-trihydroxystilbene) (**41–42**), and trans-resveratrol-3-O- $\beta$ -glucoside (trans-piceid) were quantified in *P. vera* kernel [49–51]. *P. lentiscus* leaf is a rich source of polyphenol compounds (7/5% of leaf dry weight) especially galloyl derivatives like mono, di, and tri-O-galloyl quinic acid (**43**) and monogalloyl glucose (**44**) [45].

1,2,3,4,6-Pentagalloyl glucose (**45**) and gallic acid from fruits of *P. lentiscus* were introduced as antioxidant and antimutagenic compounds [52].

Flavonoid compounds have been detected in different parts of these species. Naringenin (**46**), eriodictyol (**47**), daizein (**48**), genistein (**49**), quercetin (**50**), kaempferol (**51**), apigenin (**52**), and luteolin (**53**) were isolated from *P. vera* fruit, and quercetin-3-O-rutinoside (**54**) is the main constituent of seed [44]. Decrease in flavonoid content

of *P. vera* has been reported during the fruit ripening [51]. In addition to some known flavonoids isolated from *P. terebinthus* and *P. atlantica* fruits, 6'-hydroxyhypolaetin 3'-methyl ether (**55**) has been identified in fruits of *P. terebinthus* [46, 53]. Flavonoids were also isolated from aerial parts of *P. atlantica* and *P. lentiscus*, and quercetin-3-glucoside (**56**) was reported as the most abundant one [54]. 3-Methoxycarpachromene (**57**), a flavone with antiplasmodial activity, was isolated from aerial parts of *P. atlantica* [55].

Myricetin-3-glucoside (**58**), myricetin-3-galactoside (**59**), and myricetin-3-rutinoside (**60**) are the major flavonoid glycosides from *P. khinjuk* [54]. Myricetin derivatives also were determined as 20% of the total polyphenol amount of *P. lentiscus* leaves [45].

Anthocyanins have been reported from some *Pistacia* species. Cyanidin-3-O-glucoside (**61**), cyanidin-3-galactoside (**62**), and quercetin-3-O-rutinoside are the main anthocyanins of *P. vera* fruit [44, 56, 57]. Cyanidin-3-O-glucoside and delphinidin-3-O-glucoside (**63**) have been detected in *P. lentiscus* berries and leaves [7, 45].

**3.3. Fatty Acids and Sterols.** *Pistacia* species have oleaginous fruits considered by several researchers. The oil content in *P. vera* kernel and seed is about 50–60% [58, 59] and in ripe fruits of *P. lentiscus*, *P. terebinthus*, and *P. atlantica* is 32.8–45% [60–63]. The main fatty acid in seed and kernel of *P. vera* is oleic acid [58, 64, 65]. Oleic acid has been also determined

TABLE 2: Chemical compounds isolated from selected *Pistacia* species.

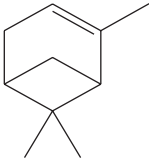
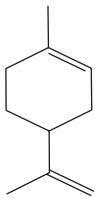
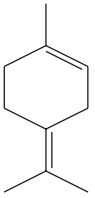
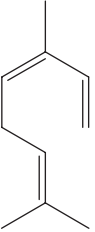
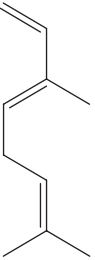
Name of compound	Structure	Species	Plant part	References
Monoterpenoids, sesquiterpenoids, and volatile oil				
1 $\alpha$ -pinene		<i>P. vera</i>	Leaf and unripe fruit Resin	[14] [12, 15]
		<i>P. terebinthus</i>	Fruit Aerial part	[16] [17]
		<i>P. terebinthus</i> var. <i>palaestina</i>	Leaf and gall	[18]
		<i>P. lentiscus</i> var. <i>chia</i>	Resin	[19]
		<i>P. lentiscus</i>	Leaf Fruit Aerial part	[20] [21] [22–24]
		<i>P. atlantica</i>	Leaf, fruit, and gall Resin	[25] [26, 27]
		2 Limonene		<i>P. vera</i>
<i>P. terebinthus</i>	Unripe and ripe fruits			[29]
<i>P. lentiscus</i>	Fruit Leaf			[28] [28, 36]
3 Terpinolene				<i>P. vera</i>
		<i>P. atlantica</i>	Leaf	[28]
4 $\alpha$ -Ocimene				
5 $\beta$ -Ocimene		<i>P. vera</i>	Leaf	[28]
		<i>P. terebinthus</i>	Unripe and ripe fruits Leaf	[18] [28]

TABLE 2: Continued.

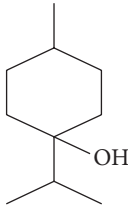
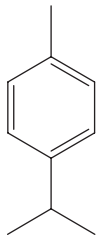
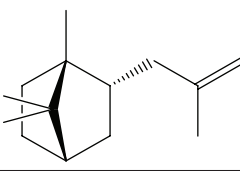
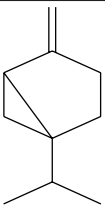
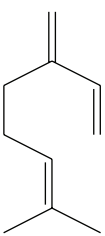
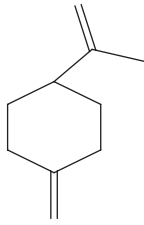
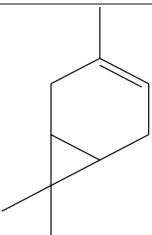
Name of compound	Structure	Species	Plant part	References
6 Terpinen-4-ol		<i>P. terebinthus</i>	Leaf	[30]
		<i>P. atlantica</i>	Unripe fruits	[31]
			Leaf	[27, 31]
		<i>P. lentiscus</i>	Aerial parts	[22]
			Leaf	[30, 35]
7 <i>p</i> -Cymene		<i>P. terebinthus</i>	Young shoots	[29]
8 Bornyl acetate		<i>P. atlantica</i>	Fruits	[27]
9 Sabinene		<i>P. atlantica</i>	Fruits	[28]
			Unripe fruits	[31]
		<i>P. lentiscus</i>	Leaf buds	[31]
			Fruits Leaf	[28]
10 Myrcene		<i>P. atlantica</i>	Unripe fruits	[31]
			Leaf	[31]
		<i>P. lentiscus</i>	Fruits	[34, 36]
			Leaf	
11 <i>p</i> -Mentha-1 (7),8 diene		<i>P. atlantica</i>	Leaf Leaf buds	[31] [31]
12 $\Delta^3$ -carene		<i>P. atlantica</i>	Unripe galls	[32]

TABLE 2: Continued.

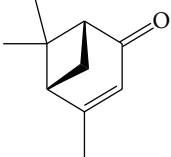
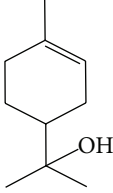
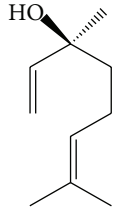
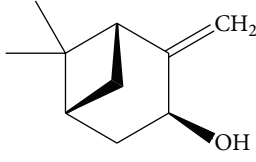
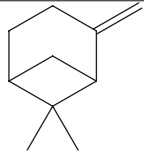
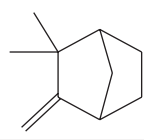
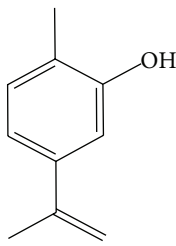
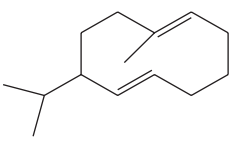
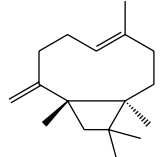
Name of compound	Structure	Species	Plant part	References
13 Verbenone		<i>P. lentiscus</i>	Mastic water Mastic oil	[33] [19]
14 $\alpha$ -terpineol		<i>P. lentiscus</i>	Mastic water Mastic oil	[33] [19]
15 Linalool		<i>P. lentiscus</i>	Mastic water	[33]
16 <i>Trans</i> -pinocarveol		<i>P. lentiscus</i>	Mastic water	[33]
17 $\beta$ -pinene		<i>P. lentiscus</i>	Resin	[30]
18 Camphene		<i>P. vera</i>	Resin	[12]
19 Carvacrol		<i>P. vera</i>	Resin	[12]
20 Germacrene-D		<i>P. lentiscus</i> <i>P. terebinthus</i>	Leaf Flowers	[28] [29]
21 $\beta$ -caryophyllene		<i>P. terebinthus</i> <i>P. lentiscus</i>	Leaf Galls	[28] [34] [24]

TABLE 2: Continued.

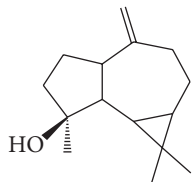
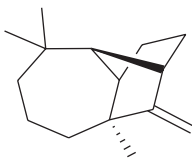
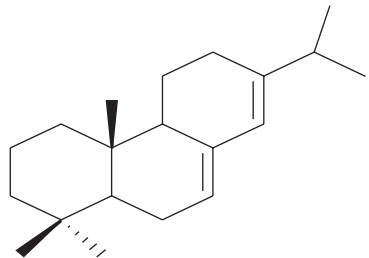
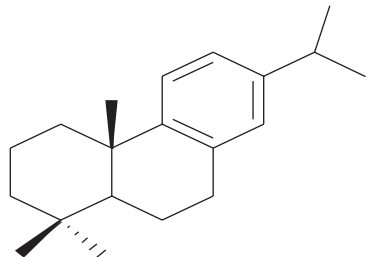
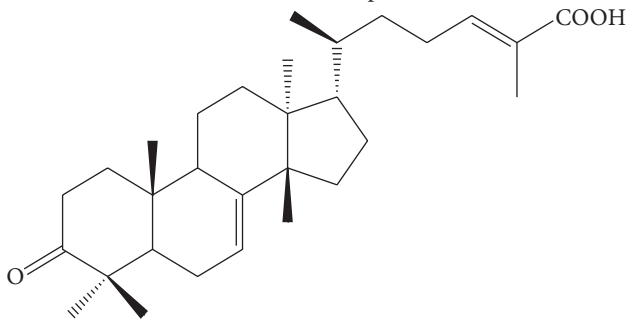
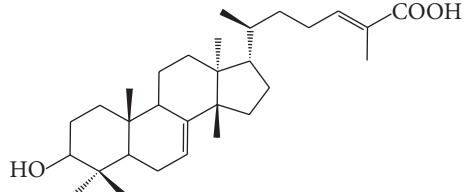
Name of compound	Structure	Species	Plant part	References
22 Spathulenol		<i>P. atlantica</i> <i>P. khinjuk</i>	Leaf Leaf	[37] [38]
23 Longifolene		<i>P. lentiscus</i>	Aerial parts	[39]
Diterpenoids				
24 Abietadiene		<i>P. vera</i>	Resin	[12]
25 Abietatriene		<i>P. vera</i>	Resin	[12]
Triterpenoids				
26 Masticadienonic acid		<i>P. lentiscus</i> <i>P. terebinthus</i> <i>P. atlantica</i>	Resin Resin Resin	[40] [41] [42]
27 Masticadienolic acid		<i>P. lentiscus</i> <i>P. terebinthus</i> <i>P. atlantica</i>	Resin Resin Resin	[40] [41] [42]



TABLE 2: Continued.

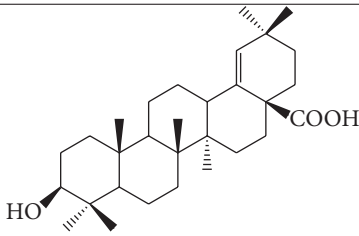
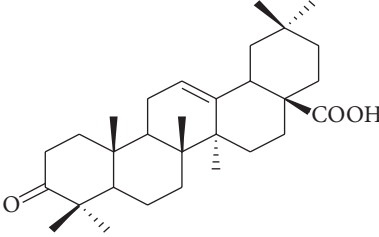
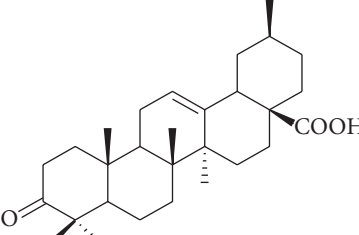
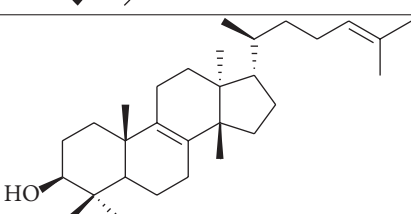
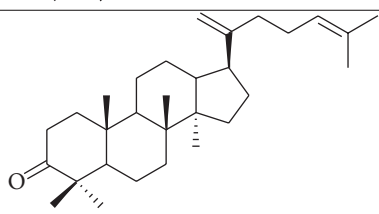
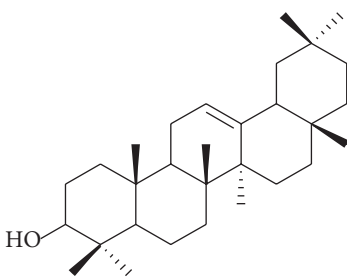
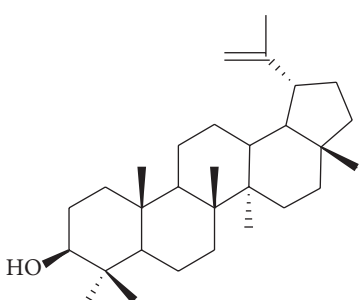
Name of compound	Structure	Species	Plant part	References
28 Morolic acid		<i>P. lentiscus</i> <i>P. terebinthus</i> <i>P. atlantica</i>	Resin Resin Resin	[40] [41] [42]
29 Oleanolic acid		<i>P. lentiscus</i> <i>P. terebinthus</i> <i>P. atlantica</i>	Resin Resin Resin	[40] [41] [42]
30 Ursonic acid		<i>P. atlantica</i>	Resin	[42]
31 Tirucallol		<i>P. lentiscus</i> <i>P. terebinthus</i>	Resin Resin	[40] [41]
32 Dammaradienone		<i>P. lentiscus</i> <i>P. terebinthus</i>	Resin Resin	[40] [41]
33 $\beta$ -Amyrin		<i>P. lentiscus</i> <i>P. terebinthus</i>	Resin Resin	[40] [41]
34 Lupeol		<i>P. lentiscus</i> <i>P. terebinthus</i>	Resin Resin	[40] [41]

TABLE 2: Continued.

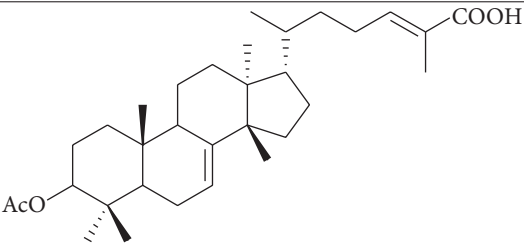
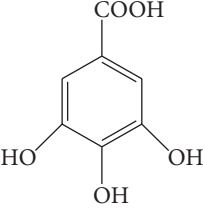
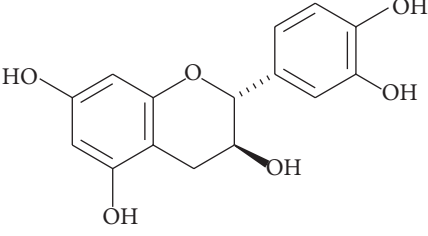
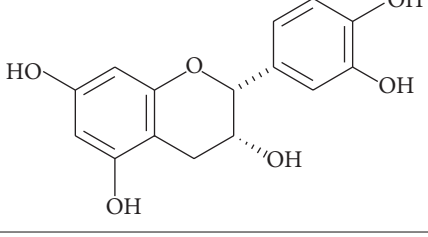
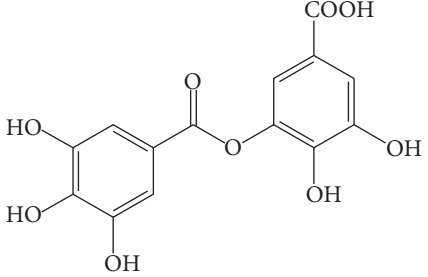
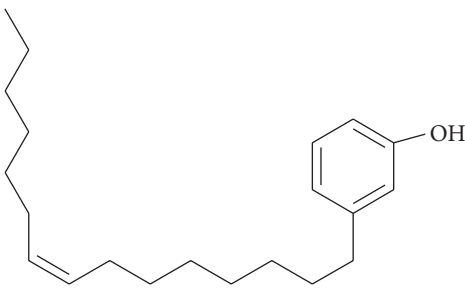
Name of compound	Structure	Species	Plant part	References
35 3-O-acetyl-3-epiisomasticadienolic acid		<i>P. atlantica</i>	Resin	[42]
36 Gallic acid	Phenolic compounds 	<i>P. vera</i> <i>P. lentiscus</i> <i>P. atlantica</i>	Seed and skin Leaf Fruit Gall and Leaf	[44] [45] [52] [46]
37 Catechin		<i>P. vera</i> <i>P. lentiscus</i>	Seed and skin Leaf	[44] [45]
38 Epicatechin		<i>P. vera</i>	Seed and skin	[44]
39 Digallic acid		<i>P. lentiscus</i>	Fruits	[47]
40 3-(8-Pentadecenyl)-phenol		<i>P. vera</i>	Kernel	[48]

TABLE 2: Continued.

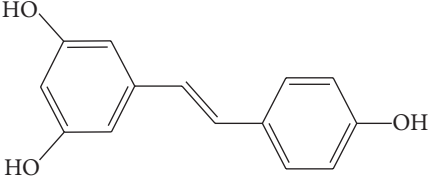
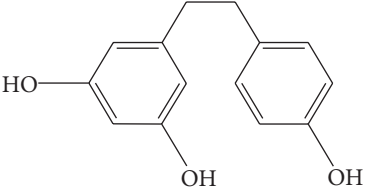
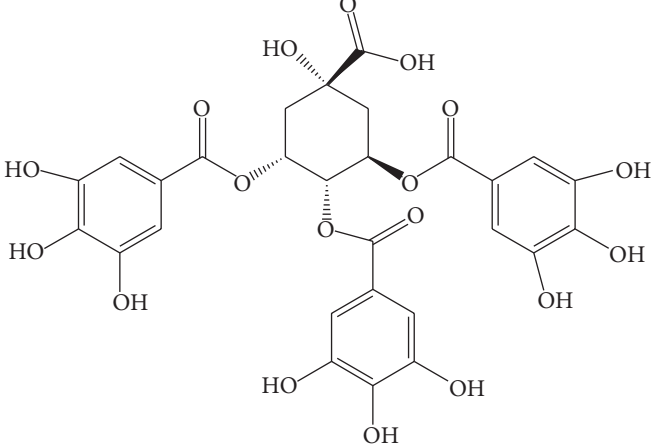
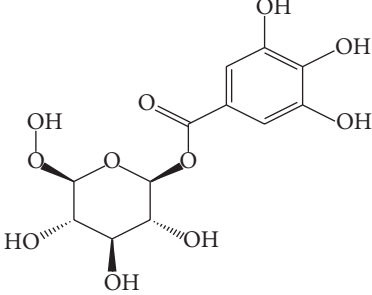
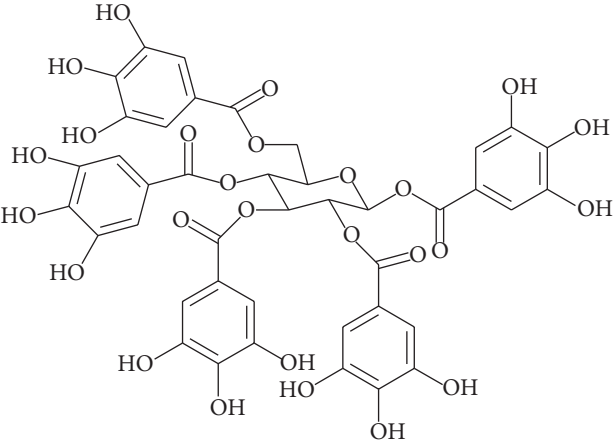
Name of compound	Structure	Species	Plant part	References
41 <i>Trans</i> -resveratrol		<i>P. vera</i>	Kernel	[49-51]
42 <i>Cis</i> -resveratrol		<i>P. vera</i>	Kernel	[49]
43 3,4,5-Tri-O-galloyl quinic acid		<i>P. lentiscus</i>	Leaf	[45]
44 Monogalloyl glucose		<i>P. lentiscus</i>	Leaf	[45]
45 1,2,3,4,6-Pentagalloyl glucose		<i>P. lentiscus</i>	Fruit	[52]

TABLE 2: Continued.

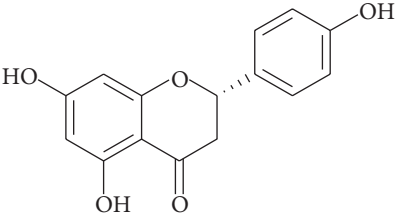
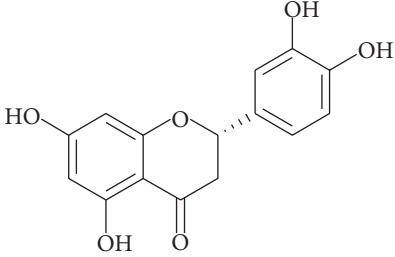
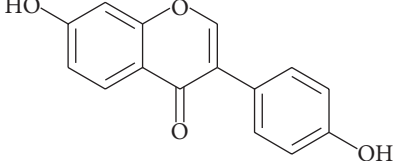
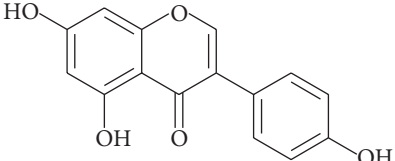
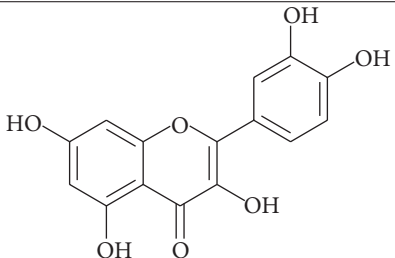
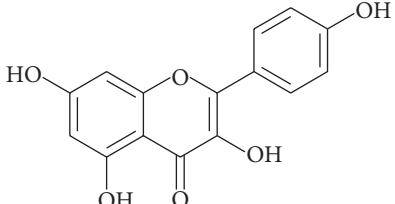
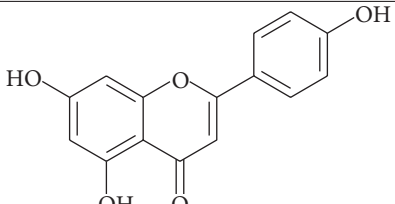
Name of compound	Structure	Species	Plant part	References
46 Naringenin		<i>P. vera</i>	Seed and skin	[44]
47 Eriodictyol		<i>P. vera</i>	Seed and skin	[44]
48 Daidzein		<i>P. vera</i>	Seed and skin	[44]
49 Genistein		<i>P. vera</i>	Seed and skin	[44]
50 Quercetin		<i>P. vera</i>	Seed and skin	[44]
51 Kaempferol		<i>P. vera</i>	Seed and skin	[44]
52 Apigenin		<i>P. vera</i>	Seed and skin	[44]

TABLE 2: Continued.

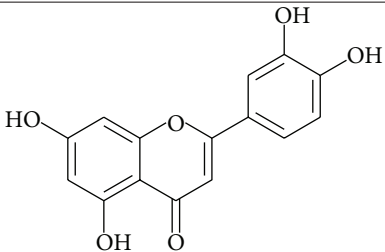
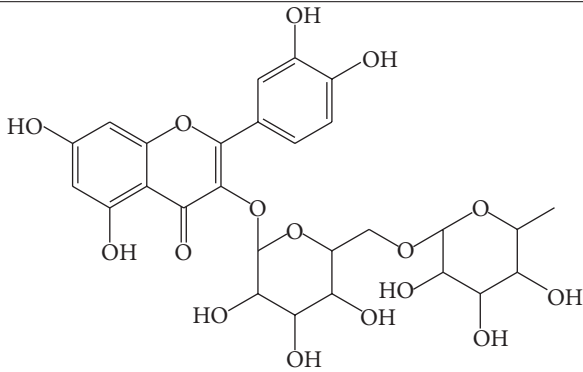
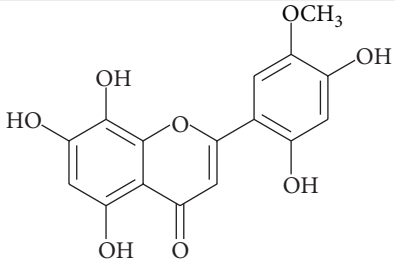
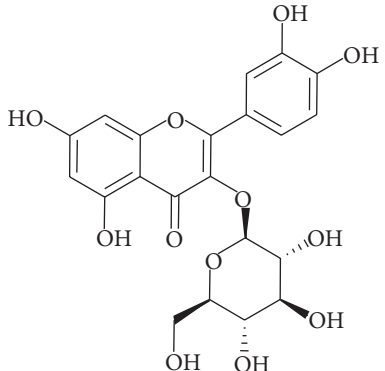
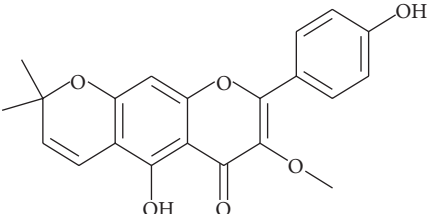
Name of compound	Structure	Species	Plant part	References
53 Luteolin		<i>P. vera</i>	Seed and skin	[44]
54 Quercetin-3-O-rutinoside		<i>P. vera</i>	Seed and skin	[44]
55 6'-Hydroxyhypolaetin 3'-methyl ether		<i>P. terebinthus</i>	Fruits	[53]
56 Quercetin-3-glucoside		<i>P. atlantica</i> <i>P. lentiscus</i>	Aerial parts	[54]
57 3-Methoxycarpachromene		<i>P. atlantica</i>	Aerial parts	[55]

TABLE 2: Continued.

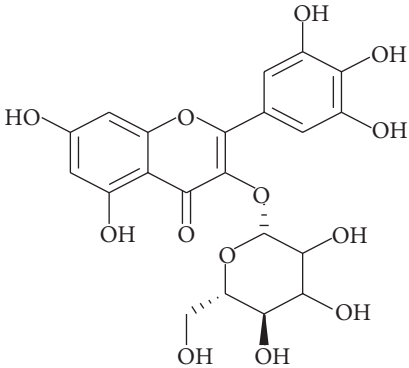
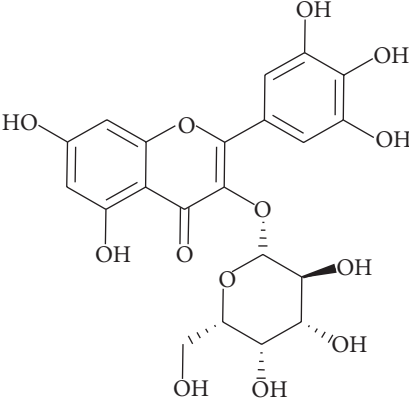
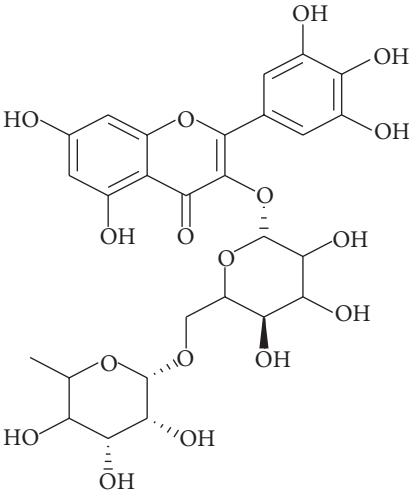
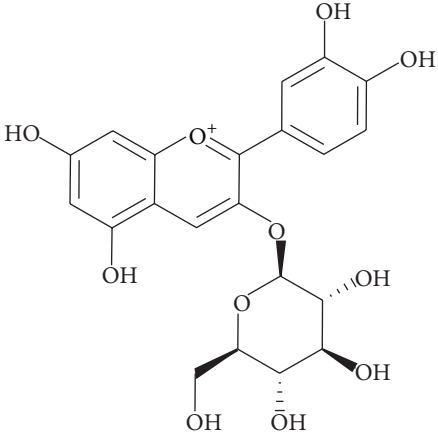
Name of compound	Structure	Species	Plant part	References
58 Myricetin-3-glucoside		<i>P. khinjuk</i>	Aerial parts	[54]
59 Myricetin-3-galactoside		<i>P. khinjuk</i>	Aerial parts	[54]
60 Myricetin-3-rutinoside		<i>P. khinjuk</i>	Aerial parts	[54]
61 Cyanidin-3-O-glucoside		<i>P. vera</i> <i>P. lentiscus</i>	Skin Nuts Berries leaves	[44] [56] [57] [7] [45]

TABLE 2: Continued.

Name of compound	Structure	Species	Plant part	References
62 Cyanidin-3-galactoside		<i>P. vera</i>	Skin Nuts	[44, 56] [57]
63 Delphinidin-3-O-glucoside		<i>P. lentiscus</i>	Berries Leaves	[7] [45]

as the most abundant fatty acid in oil of *P. atlantica* and *P. terebinthus* fruits [62, 66, 67]. Increase of oleic acid and decrease of linoleic acid have been recorded during ripening of *P. lentiscus* fruits [60]. Other fatty acids identified in these species are linolenic, palmitic, palmitoleic, stearic, myristic, eicosanoic, behenic, lignoceric, arachidonic, pentadecanoic, hexadecanoic, octadecanoic, and margaric acid [58, 66, 68].

The most abundant sterol reported in fruits of *P. vera*, *P. atlantica*, *P. lentiscus*, and *P. terebinthus* is  $\beta$ -sitosterol followed by campesterol,  $\Delta^5$ -avenasterol, stigmasterol, brassicasterol, and cholesterol [59, 60, 69, 70].

The oil from fruits of *P. atlantica*, *P. lentiscus*, and *P. terebinthus*, in addition to its desirable odor and taste, has been recommended as a new source for production of vegetable oils concerning the high amount of mono-unsaturated and omega-3 fatty acids like oleic acid and linolenic acid and high quantity of phytosterols like  $\beta$ -sitosterol [60, 68].

**3.4. Miscellaneous.** Chlorophylls *a* and *b* and lutein are the major colored components of *P. vera* nuts [56]. Pheophytin,  $\beta$ -carotene, neoxanthin, luteoxanthin, and violaxanthin were also determined in different samples of *P. vera* nuts [71].  $\alpha$ -tocopherol was determined in leaves of *P. lentiscus*, *P. lentiscus*

var. *chia*, and *P. terebinthus* [72]. Tocopherols and tocotrienols are the most abundant constituents of unsaponifiable matter of *P. atlantica* hull oil [73]. Different isomers of tocopherol, tocotrienol, and plastochromanol-8 have been identified in seed oil of *P. terebinthus* [70]. Evaluating the nutritional composition of *P. terebinthus* fruits illustrates the richness of this fruit in protein, oil, minerals, and fiber [62, 68].

#### 4. Pharmacological Aspects

Different pharmacological activities of five mentioned *Pistacia* species have been described in detail in Table 3.

**4.1. Antioxidant Activity.** Different parts and constituents from *P. lentiscus* have been shown in vitro radical scavenging properties [23, 47, 52, 74–76]. *Pistacia lentiscus* var. *chia* and *P. terebinthus* var. *chia* resins were effective in protecting human LDL from oxidation in vitro [77]. *P. atlantica* leaf and fruit have shown antioxidant activity similar to or significantly higher than those of standard antioxidant compounds in different in vitro antioxidant assays [78–80]. However, the essential oil from *P. atlantica* leaf showed weak antioxidant activity in DPPH test compared to synthetic antioxidants

TABLE 3: Pharmacological activities of selected *Pistacia* species.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
			In vitro DPPH method		1, 3, 10, 30, and 100 µg/mL	Dose dependent radical scavenging activity of GA (IC50: 2 µg/mL) and PGA (IC50: 1 µg/mL)	
		Fruits	Xanthine oxidase inhibition	Polyphenols: gallic acid (GA) and 1,2,3,4,6 pentagalloyl-glucose (PGA)	100, 200, and 300 µg/mL	↑formation of uric acid and superoxide anions (O <sub>2</sub> <sup>-</sup> ) by increasing concentrations of both GA and PGA	[52]
			Inhibition of lipid peroxidation induced by H <sub>2</sub> O <sub>2</sub> in K562 cell line		200, 400, and 800 µg/mL for GA and 100, 200, and 400 µg/mL for PGA	Dose dependent inhibition by GA (IC50: 220 µg/mL) and PGA (IC50: 200 µg/mL)	
			Reducing power	Seven different extracts (1) Ethanol, (2) Ethyl acetate, (3) Aqueous/ethyl acetate, (4) Hexane, (5) Aqueous/hexane, (6) Chloroform, (7) Aqueous/chloroform	100 µg/mL	Higher activity of aqueous fractions from hexane and chloroform than standards (BHA and α-tocopherol)	
			Linoleic acid peroxidation	(3) Aqueous/ethyl acetate, (4) Hexane, (5) Aqueous/hexane, (6) Chloroform, (7) Aqueous/chloroform	100 µg/mL	Inhibition of linoleic acid peroxidation by aqueous extracts from chloroform and hexane comparable to those of the standard (BHA)	
	<i>P. lentiscus</i>	Leaf	DPPH method	(4) Hexane, (5) Aqueous/hexane, (6) Chloroform, (7) Aqueous/chloroform	10-100 µg/mL	High scavenging activity (90%) equivalent to that of the standard BHA (89%) by all extracts except chloroform	[75]
			Scavenging activity against hydrogen peroxide	(6) Chloroform, (7) Aqueous/chloroform	100 µg/mL	High scavenging capacity against H <sub>2</sub> O <sub>2</sub> comparable to standards (α-tocopherol and BHA)	[74]
			DPPH method	Essential oil	0.2, 0.4, 1.0, 2.0, and 4.0 mM	Antioxidant activity ranged between 0.52 and 4.61 mmol/L	[23]
		Aerial parts	DPPH method	Methanolic extracts	100, 80, 50, 30, 20, 10, and 5 mg/L	IC50 ranged between 5.09 and 11.0 mg/L	
			FRAP assay		5000 mg/L	Activity ranged between 84.6 and 131.4 mmol Fe2+/L plant extract; IC50: 5.09-11.0 (mg/L)	
	<i>P. lentiscus</i> var. <i>chia</i>	Resin	Oil oxidation assay by the oven test	Resin solution in dichloromethane	0.05, 0.1, and 0.15% w/w	Significant antioxidant activity	[149]
			ABTS		0.05, 0.1, 0.15, and 0.2 mg/mL	Free radical scavenging activity towards the ABTS + radical was 99% at 0.2 mg/mL	
Antioxidant		Fruit	Xanthine oxidase (XO) inhibition and superoxide scavenging activity	Digallic acid	50, 100, and 150 µg/mL	21% XO inhibitory activity at 150 µg/mL; 28% reduction of superoxide anion activity	[47]
	<i>P. lentiscus</i>		Electron-spin resonance		200, 400, and 800 µg/mL	↓lipid peroxidation (IC50: 178 µg/mL)	
			Spectroscopy for the determination of hydroxyl radical by Fenton reaction		ND	Effectively scavenged hydroxyl radical generated by the Fenton reaction	[76]
		Gum	Nitrate/nitrite colorimetric assay	Mastic in water	0-3 mg/mL	No nitric oxide scavenging activity	



TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
	<i>P. lentiscus</i> var. <i>chia</i> , <i>P. terebinthus</i> var. <i>chia</i>	Gum	Copper-induced LDL oxidation	Hexane and methanol/water extracts	2.5, 5, 10, 25, and 50 mg/2 mL	LDL protective activity; methanol/water extract of <i>P. lentiscus</i> showed the most LDL protection	[77]
	<i>P. lentiscus</i>	Leaf	Reduction power activity	Ethanol extract	0.25; 0.5; 0.75; 1; 2; 3 mg/mL	Reducing power comparable to ascorbic acid	[88]
	<i>P. atlantica</i>	Leaf	Pyrogallol autoxidation method	Ethanol extracts	ND	Superoxide anions scavenging activity	[88]
	<i>P. atlantica</i> subsp. <i>mutica</i>	Hull	Reduction power activity	Ethanol extracts	0.25; 0.5; 0.75; 1; 2; 3 mg/mL	Reducing power close to values observed by ascorbic acid	[88]
			Pyrogallol autoxidation method		ND	Superoxide anions scavenger at a concentration as low as 0.0625 mg/mL	
			FRAP test	The unsaponifiable matter (USM) of fruits	100 mg in 10 mL of <i>n</i> -hexane	Significant reducing power; the highest reducing power amongst the USM fractions belonged to the tocopherols and tocotrienols and linear and triterpene alcohols respectively	[80]
			DPPH radical-scavenging assay	hull oil	ND	EC50 value significantly lower than $\alpha$ -tocopherol	
			Oven test		ND	Significant stabilizing effect	
			(1) Reducing power			(1) Reducing power of significantly higher than $\alpha$ -tocopherol and BHT and nearly similar to BHA	
			(2) Chelating abilities on metallic ions		(1) 20–100 $\mu$ g/mL	(2) The chelating activity of 1.0 mg/mL was nearly fourfold less than EDTA at 0.037 mg/mL and has slightly effective capacity for iron binding	
			(3) Radical scavenging		(2) 0.25, 0.50, 0.75, and 1.0 mg/mL	(3) 85% inhibition rate at 15 $\mu$ g/mL, nearly similar to ascorbic acid and BHA	[78]
	<i>P. atlantica</i>	Leaf	Activity (DPPH)	Decoction	(3) 5–25 $\mu$ g/mL	(4) Higher antioxidant activity than $\alpha$ -tocopherol and similar to BHA, BHT, and trolox	
			(4) The total antioxidant activity (thiocyanate method in linoleic acid emulsion)		(4) 100 $\mu$ g/mL	(5) Concentration-dependent scavenging compared to BHA, BHT, and $\alpha$ -tocopherol	
			(5) Hydrogen peroxide scavenging activity		(5) 100 $\mu$ g/mL		
	<i>P. atlantica</i> subsp. <i>mutica</i>	Fruit hull	Rancimat test	<i>n</i> -Hexane extract	Different percentages (up to 15%)	The antioxidant activity of hull oil was exactly the same as that of TBHQ at low concentrations	[79]
	<i>P. atlantica</i>	Leaf	DPPH test	Essential oil	50 $\mu$ L	Weak radical scavenging activity	[32]
			FRAP test		ND	Higher antioxidant capacity relative to ascorbic acid	
	<i>P. vera</i>	Fruit hull	Oven test	Water and methanol extracts	0.02%, 0.04%, and 0.06% in soybean oil	Effective in retarding oil deterioration at 60° C; at concentration of 0.06%, similar to BHA and BHT added at 0.02%.	[81]
			ABTS radical cation decolorization assay	Methanol/water or Dichloromethane	ND	The antioxidant activity of the lipophilic extract was much lower than hydrophilic one	[82]
		Kernel	Lipid peroxidation (TBARS assay)	Hydrophilic extract	0.25, 0.5, or 1.0 mg/mL	Radical scavenging activity in a dose-dependent manner	
	<i>P. vera</i> L., var. <i>Bronte</i>		Copper-mediated LDL oxidation	Hydrophilic extract	Extracts from 30, 60, or 100 $\mu$ g of nut	Inhibition of LDL oxidation	
			DPPH assay		0.050–12.00 mg/mL	Radical scavenging activity	
		Seed and skin (hull)	Trolox equivalent antioxidant capacity (TEAC) assay (ABTS radical)	Methanol/water extract	ND	Antioxidant power: 0.015 $\pm$ 0.001 and 2.19 $\pm$ 0.14 mmol Trolox/g of seeds and skins, respectively	[44]
			Scavenging activity against the superoxide anion		ND	IC50 of 3.25 $\pm$ 0.19 and 0.25 $\pm$ 0.02 mg for seeds and skins, respectively	

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
	<i>P. vera</i>	Gum	TBARS and FRAP in rat DPPH assay	Extract	0.1–0.5 g/kg 1, 1.5, 2.5, 3.5 and 4 µg/mL	↓brain MDA level by 63% and ↑antioxidant power of brain by 235% Concentration-dependent radical scavenging activity	[83]
		Hull	ABTS assay β-carotene bleaching method	Aqueous	ND 0.48–9.5 µg/mL	Scavenging capacity of crude and purified extracts was higher than standards compounds (TBHQ and BHT) Concentration-dependent antioxidant capacity	[150]
		Leaf	Trolox equivalent antioxidant capacity assay (ABTS/K2S8O2 method)	Ethanol-water extract	ND	Considerably higher antioxidant activity compared with BHA and ascorbic acid	[84]
	<i>P. terebinthus</i>	Fruits	DPPH test	Acetone and methanol extracts	25, 50 and 100 µg/mL	High radical scavenging activity	[53]
Total antioxidant activity in β-carotene-linoleic acid system			25, 50 and 100 µg		Isolated pure 60-hydroxyhypolaetin-30-methyl Ether showed higher antioxidant activity than both extracts and BHT		
Superoxide anion scavenging activity			50 µg		Both extracts had scavenging activity near to ascorbic acid; higher activity of methanol extract than acetone extract		
FRAP			0.2–1 µg/mL		Higher reducing power of methanol extract than α-tocopherol; acetone extract reducing power was equal to that of α-tocopherol		
			Metal chelating activity		1000–4000 µg/mL	Methanol extract had higher activity than acetone extract	
			DPPH radical scavenging activity			High scavenging effect especially at 2000 µg/mL	
		Fruits and 4 terebinth coffee brands	DMPD radical scavenging activity H <sub>2</sub> O <sub>2</sub> radical scavenging activity	Ethyl acetate and methanol extracts	250, 500, 1000 and 2000 µg/mL	Scavenging effect lower than that of quercetin	[85]
			Metal-chelation effect			Inactive in scavenging H <sub>2</sub> O <sub>2</sub> radical	
			FRAP assay PRAP assay			Remarkable metal-chelation properties as compared to EDTA	
						High reducing power	
						High reducing power	
			Aflatoxin BI (AFBI)-induced mutagenicity in <i>S. typhimurium</i> TA 100	Essential oil	250, 500 and 1000 µg/plate	Mutagenic inhibition of 76.7% by 250, 82.8% by 500, and 96.5% by 1000 µg/plate	[86]
Antimutagenic	<i>P. lentiscus</i>	Leaf	(AFBI)-induced mutagenicity in <i>S. typhimurium</i> TA100 or TA98	Essential oil	0.3, 250, 500, 1000 µg/plate	In TA100: 76, 82.8, and 96.5% mutagenic inhibition rate for 250, 500, and 1000 µg/plate, respectively; in TA98: 99 and 100% mutagenic inhibition rate with 250 and 500 µg/plate	
				Aqueous extract	0.3, 50, 300, 600 µg/plate	50 µg/plate: 23% inhibition in TA100 and 52.2% in TA98; 300 and 600 µg/plate: 67.7 and 87.8% for TA100 and 58–76.8% for TA98	[87]
				Flavonoid-enriched extract extracts	50, 300, 600 µg/plate	TA100: 47, 75.3, and 88.6% inhibition by 50, 300, and 600 µg/plate, respectively; TA98: 62.5, 77, and 93.5% inhibition by 50, 300, and 600 µg/plate, respectively	

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
Antimicrobial and antiviral	<i>P. lentiscus</i>	Leaf	Sodium azide-induced mutagenicity in <i>S. typhimurium</i> TAI535 and TAI100	Essential oil	1.5, 10, 15, 30 µg/Plate	TAI00: 79, 83, and 94% inhibition by 10, 15, and 30 µg/plate, respectively; TAI535: 62, 76, and 93% inhibition by 10, 15, and 30 µg/plate, respectively	[86]
				Aqueous extract	1.5, 50, 300, 600 µg/plate	TAI00: 92, 96, and 98% inhibition by 50, 300, and 600 µg, respectively; TA 1535: 62, 80, and 94% for the same concentrations	
				Flavonoid-enriched extract extracts	50, 300, 600 µg/plate	50 and 300 µg/plate: from 54 to 68% inhibition in TAI535 and from 84 to 93% in TAI00	
		Disc diffusion	Disc diffusion	Essential oil	0.03, 0.15, 0.62, 2.5, 10.0, 40.0 mg/mL	Noticeable activity against <i>S. enteritidis</i> (MIC: 30 µg/mL) and <i>S. aureus</i> (30 µg/mL); less important activity against <i>S. typhimurium</i> , (MIC: 150 µg/mL); No significant inhibitory activity towards <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , and <i>Enterococcus faecalis</i>	[86]
		Disc diffusion	Disc diffusion	Ethanol extract	5 and 10 µL	No effect on <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i> .	[88]
		Disc diffusion	Disc diffusion	Ethanol extract	50, 100, 500 µL, and 1 mL	Significant inhibition against <i>Candida albicans</i> , <i>Staphylococcus aureus</i> , and <i>Salmonella typhi</i>	[88]
		Disc diffusion	Disc diffusion	Aqueous extract	ND	Inhibiting activity on <i>Trichoderma sp</i> and <i>Fusarium sp</i>	[88]
		Disc diffusion	Disc diffusion	Total oligomer flavonoid-enriched extract	ND	Most active against <i>S. typhimurium</i> , (MIC: 4 µg/mL), significant inhibitory activity towards <i>P. aeruginosa</i> and <i>S. enteritidis</i> (MIC: 40 µg/mL), and no activity against <i>S. aureus</i> , <i>E. coli</i> , and <i>Ent. faecalis</i> up to 1000 µg/mL	[87]
		Microdilution agar	Microdilution agar	Essential oil	ND	TOF extract exhibited antibacterial activity only against <i>S. typhimurium</i> (MIC: 100 µg/mL)	[19]
		<i>P. lentiscus</i> var. <i>chia</i>	Gum	Disc diffusion	Essential oil and its fractions and components	Essential oil	ND
Mastic gum water (MWR) and its major constituents	MWR (58 mg/mL), (-)-trans-pinocarveol (13 mg/mL), (-)-linalool (37.6 mg/mL), (±)-linalool (36.6 mg/mL), (-)-verbenone (29.5 mg/mL), and (+)-α-terpineol (29.2 mg/mL)					The broadest average inhibition zones were for <i>E. coli</i> and <i>S. aureus</i> by (+)-α-terpineol and (±)-linalool compared to the positive control (gentamicin 10 µg): significant antifungal activity against <i>Candida albicans</i> by MWR	
Microdilution	Gum	Microdilution	Microdilution	Microdilution	4%, 2%, 1%, 0.5%, 0.25%, 0.125%, 0.063%, and 0.032% (v/v)	The most potent antimicrobial constituents were (±)-linalool and α-terpineol against <i>E. coli</i> and <i>S. aureus</i> . Significant antifungal activity of MWR, (±)-linalool, (-)-verbenone, and (+)-α-terpineol against <i>C. albicans</i>	[33]

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
	<i>P. lentiscus</i>	Gum	ND	Liquid mastic	2% liquid mastic	Activity against <i>Porphyromonas gingivalis</i> and <i>Prevotella melaninogenica</i>	[76]
			Human T-cell leukemia MT-4 cells infected with HIV-1 <sub>IIIB</sub> ; viable cell number determination by MTT assay	Solid and liquid mastic	Solid mastic: 0–200 µg/mL; liquid mastic: 0–0.0006%	Neither solid nor liquid mastic had any anti-HIV activity compared to positive controls	
	<i>Pistacia lentiscus</i> var. <i>chia</i>	Gum	Microdilution	Total mastic extract without polymer (TMEWP), acidic and neutral fractions	MEWP: 0.049 to 1.560 mg/mL, fractions: 0.060 to 1.920 mg/mL	The acidic fraction exhibited the highest activity against <i>Helicobacter pylori</i> followed by the TMEWP and neutral fraction	[33]
			In vivo administration of extract in infected mice with <i>H. pylori</i>	Total mastic extract without polymer (TMEWP)	180 µg/mL	Moderately reduced <i>H. pylori</i> colonization in the antrum and corpus of the mice stomach. Visible reduction in <i>H. pylori</i> colonization observed in histopathology evaluations	
	<i>P. lentiscus</i> , <i>P. atlantica</i> (sp. <i>cabulica</i> , <i>kurdica</i> , and <i>mutica</i> )	Gum	Broth microdilution	Isolated components of the acidic fractions of the gum	ND	The MIC values for the components ranged from 0.1 to 50 µg/mL against the strains of <i>H. pylori</i> and all Gram-negative bacteria including <i>Escherichia coli</i> , <i>Salmonella typhimurium</i> , <i>Serratia marcescens</i> , <i>Pseudomonas aeruginosa</i> , <i>Alcaligenes faecalis</i> , <i>Enterobacter aerogenes</i> , <i>Pseudomonas fluorescens</i> , <i>Porphyromonas gingivalis</i> , and <i>Proteus vulgaris</i> and ranged from 2 to 100 µg/mL against Gram-positive bacteria including <i>Bacillus cereus</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus faecalis</i> , <i>Staphylococcus epidermidis</i> , <i>Bacillus subtilis</i> , and <i>Corynebacterium sp</i>	[151]
	<i>P. atlantica</i> (sp. <i>kurdica</i> )	Gum	ND	Essential oil, α-pinene	ND	Against all tested bacteria mentioned in previous row. MIC values for essential oil and pure α-pinene ranged 500–1000 mg/mL	[152]
		Leaf and twig	Modified [ <sup>3</sup> H]-hypoxanthine incorporation assay	Flavone 3-methoxycarboxymethane from ethyl acetate extract	0.8 and 4.9 µg/mL	IC50 of 3.4 µM against <i>P. falciparum</i> K1 strain where the positive controls artemisinin and chloroquine had IC50s of 3.6 and 89 nM, respectively	[55]
		Leaf and fruit derm	Disk diffusion method	Methanol, ethanol, ethanol + water, and water extracts	25, 50 and 75 mg/mL	Dose dependent activity against <i>E. coli</i> , <i>Staphylococcus aureus</i> , and <i>Staphylococcus epidermidis</i> ; less activity in comparison with gentamicin (10 µg/disk), tobramycin (10 µg/disk), and kanamycin (30 µg/disk)	[91]
	<i>P. atlantica</i>	Leaf	Disc diffusion	Ethanol extract	5 and 10 µL	<i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i> were not sensitive to the extract. <i>Candida albicans</i> , <i>Staphylococcus aureus</i> , and <i>Salmonella typhi</i> showed a sensitizing effect at the 5 µL and a very significant effect at 10 µL	[88]
			Disc diffusion	Ethanol extract	(50, 100, 500 µL, and 1 mL) of ethanolic extract (0.338 g/mL)	No inhibiting activity was observed against <i>Aspergillus flavus</i> , <i>Rhizopus stolonifer</i> , <i>Trichoderma sp.</i> , <i>Fusarium sp.</i> and <i>Aspergillus flavus</i>	
		Gall	Disc diffusion	Aqueous extract	4.9 mg	Activity against the <i>Bacillus</i> species and <i>Pseudomonas aeruginosa</i>	[92]
		Leaf and gall	Disc diffusion	Essential oils	Final 0.1% v/v	Delayed not block fungal growth in <i>Fomitopsis pinicola</i> and <i>Penicillium sp.</i> by volatile constituents of galls; volatile constituents of leaf inhibited only the growth of <i>Penicillium sp</i>	

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
		Gum	Agar disc diffusion	Essential oil	$10^{-1}$ , $10^{-2}$ , $10^{-3}$ , and $10^{-4}$ $\mu\text{g/mL}$	Most active against <i>E. coli</i> followed by <i>S. aureus</i> and <i>S. pyogenes</i> .	[90]
			Inhibitory quantity (MIQ) method		0.5, 1, 1.5, and 2 $\mu\text{g/mL}$	<i>S. aureus</i> and <i>S. pyogenes</i> were susceptible to 0.5 $\mu\text{g/mL}$ , and <i>E. coli</i> was tolerant to this concentration	
			Maruzzella method		$10^{-1}$ , $10^{-2}$ , $10^{-3}$ $\mu\text{g/mL}$	<i>E. coli</i> , <i>Staphylococcus aureus</i> , and <i>Streptococcus pyogenes</i> were sensitive to $10^{-1}$ $\mu\text{g/mL}$ .	
	<i>P. atlantica</i> var. <i>kurdica</i>	Gum	Mice infected with <i>Leishmania major</i>	Gum	Locally rubbed on lesions	↓Skin lesion size in mice infected with <i>L. major</i> compared with control ( $P < 0.01$ ); ↓number of parasitologically positive mice ( $P < 0.05$ )	[93]
		Leaf	Microdilution	Hydroalcoholic extract	0.024, 0.049, 0.097, 0.19, 0.78, 1.56, and 25 mg/mL (for <i>S. aureus</i> ) 0.049–12.5 mg/mL (for <i>E. coli</i> )	Activity against <i>S. aureus</i> with a MIC: $\leq 1.56$ mg/mL. No antimicrobial effect on <i>E. coli</i> .	[84]
	<i>P. terebinthus</i>	Gum	Disc diffusion, microdilution	Essential oil and gum smoke	ND	Activity of essential oil against all tested bacteria including <i>Bacillus subtilis</i> , <i>Salmonella typhi</i> , <i>Escherichia coli</i> , <i>Staphylococcus epidermidis</i> , and <i>Pseudomonas aeruginosa</i> ; activity of nonpolar smoke fraction on all of strains especially on <i>S. dysenteriae</i> , <i>E. coli</i> , <i>B. subtilis</i> , and <i>P. aeruginosa</i>	[140]
		Not mentioned	Disc diffusion, microdilution	Ethanol extract and its fractions	ND	Active against Gram-positive and Gram-negative bacteria especially <i>n</i> -butanolic fraction	[153]
	<i>P. khinjuk</i>	Leaf	Microdilution	Chloroform, ethyl acetate, ethyl alcohol, and diethyl ether extracts	ND	Activity against bacteria including <i>Bacillus subtilis</i> , <i>Enterococcus faecalis</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i> , and <i>Klebsiella pneumoniae</i> (MIC = 0.02–0.5 mg/mL) and fungi including <i>Candida albicans</i> and <i>Saccharomyces cerevisiae</i> (MIC = 0.06–0.4 mg/mL). Chloroform extract inhibited growth of fungi more than others	[38]
		Leaf, fruits derm	Disc diffusion	Methanolic extract	25, 50, 75 mg/mL	Hydroalcoholic extract of fruits derm on <i>E. coli</i> , water extract on <i>S. epidermidis</i> , and methanolic extract on <i>S. aureus</i> (all in 75 mg/mL) had higher antibacterial activity than tobramycin and same as gentamicin and kanamycin	[91]
		Leaf, branch, stem, seed	In vitro study on four parasitic protozoa	Lipophylic extracts	0.8 to 9.7 $\mu\text{g/mL}$	No inhibitory activity against <i>Trypanosoma brucei rhodesiense</i> Not any significant inhibitory potential against <i>Trypanosoma cruzi</i> Remarkable activity of branches extract at 4.8 $\mu\text{g/mL}$ against <i>Leishmania donovani</i>	[94]
	<i>P. vera</i>	Gum	Hole-plate, agar dilution	Essential oil	1/10, 1/20, 1/40, 1/80, and 1/100 v/v	Dried leaf extract displayed notable activity against <i>Plasmodium falciparum</i> at 4.8 $\mu\text{g/mL}$	[15]
			Agar-disc diffusion, broth microdilution, and broth susceptibility	Essential oil	of 2 and 4 $\mu\text{L}$	All isolates of <i>Helicobacter pylori</i> were sensitive to the essential oil (MIC: 1.55 $\mu\text{g/mL}$ ) Dose dependent activities against <i>Corynebacterium xerosis</i> , <i>Bacillus brevis</i> , <i>B. megaterium</i> , <i>Mycobacterium smegmatis</i> , <i>St. aureus</i> , <i>Klebsiella oxytoca</i> , <i>Enterococcus faecalis</i> , <i>Micrococcus luteus</i> , <i>Escherichia coli</i> , <i>Yersinia enterocolitica</i> , <i>Kluveromyces fragilis</i> , <i>Rhodotorula rubra</i> , and <i>Candida albicans</i>	[12]

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
		Hull	Disk diffusion test Agar dilution method	Aqueous	1200 µg/plate 0.5 to 10 mg/mL	Gram positive bacteria were the most sensitive	[150]
		Leaf, branch, stem, kernel, shell skins, and seeds	Microdilution In vitro antiviral assay	Lipophylic extracts	256 and 512 mg/mL	Greater activity against Gram positive bacteria than Gram-negative; remarkable antifungal activity against <i>C. albicans</i> and <i>C. parapsilosis</i> Extracts of shell skin and fresh kernel had significant activity against <i>Parainfluenza virus</i> and <i>Herpes simplex virus</i> same as the acyclovir	[89]
			Phospholipase A2 (PLA2) induced hind-paw mouse edema		200 mg/kg	Inhibition of edema	
			Ethyl phenylpropiolate (EPP) induced mouse ear edema		1 mg/ear	Inhibition of edema by 44%.	
			12-O-Tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema	Methanolic extract	1 mg/ear	Nonsignificant effect	[95]
			Mouse ear edema induced by multiple topical applications of TPA		1 mg/ear	58% inhibition of chronic inflammatory swelling	
			In vitro phospholipase A2 activity assay		ND	↓activity of the enzyme by 75%	
			Myeloperoxidase assay		ND	↓activity of the enzyme by 73%	
			Phospholipase A2 (PLA2)-induced hind-paw mouse edema		30 mg/kg	Inhibition of edema by all triterpenes	
			Ethyl phenylpropiolate (EPP) induced mouse ear edema	Masticadienonic acid, masticadienolic acid, and morolic acid from methanolic extract	1 mg/ear	31% and 38% nonsignificant inhibition of edema by masticadienolic acid and morolic acid, whereas masticadienonic acid was inactive	[95]
Anti-inflammatory	<i>P. terebinthus</i>	Gall	Mouse ear edema induced by multiple topical applications of TPA Myeloperoxidase assay Inhibition of the production of LTB4 from rat polymorphonuclear leukocytes (PMNL) Ethyl phenylpropiolate-induced mouse ear oedema Mouse ear edema induced by TPA Mouse edema induced by DPP		0.3 mg/ear 10-100 µg/mL 12.5-100 µM	Inhibition of swelling and neutrophil infiltration by all compounds 80% inhibition of enzyme activity by all the compounds Inhibition of leukotriene B4 production in rat PMNL by all compounds	
			Delayed type hypersensitivity induced by fluorobenzene in mouse ear Mouse ear inflammation induced by multiple topical applications of TPA	Oleanolic acid and its semisynthetic 3-oxo-analogue	1 mg/ear 0.5 mg/ear 0.5 mg/ear	No activity on the edema A nonsignificant 28% inhibition ↓swelling by 40% similar to standard (carbamazepine)	[95]
				Oleanolic and oleanonic acids	0.5 mg/ear 0.3 mg/ear	Oleanonic acid: ineffective at both 24 and 96 h; oleanolic acid: ↓edema nonsignificantly at 96 h by 32% Oleanonic acid: significant effect with 45% inhibition; oleanolic acid: inactive	

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
			Myeloperoxidase assay		ND	Inhibition of neutrophil infiltration by oleoanolic and oleanolic 84% and 67%, respectively	
			Phospholipase A2-induced hind paw mouse edema		30 mg/kg	↓edema by both compounds	
			Bradykinin-induced mouse paw edema	Oleoanolic acid	30 mg/kg	↓edema by 61%	
			Inhibition of leukotriene B4 production from rat polymorphonuclear leukocytes		ND	↓leukotriene B4 (IC50: 17 μM)	
			Carrageenan-induced hind paw edema	Ethanolic and aqueous extracts	250, 500 mg/kg	Among all extracts, only the oleoresin exhibited a dose-dependent anti-inflammatory activity	[146]
	<i>P. vera</i>	Fruits, leaf, branches, peduncles, and oleoresin	p-Benzoquinone-induced abdominal constriction test in mice		250, 500 mg/kg	Among all extracts, only the oleoresin displayed antinociceptive activity with 32.1% inhibition at 500 mg/kg and 21.7% inhibition at 250 mg/kg	
			Hot plate test	Aqueous extract, ethanolic extract	0.4 and 0.5 g/Kg	Dose-dependent antinociceptive activity after 30–60 min of treatment	
		Leaf	Xylene-induced ear edema	Aqueous extract	0.4, 0.16, 0.28 g/kg	Significant anti-inflammatory activities	[97]
			Chronic anti-inflammatory activity (granuloma pouch method)	Aqueous extract, ethanolic extract	0.4 g/Kg 0.35, 0.5 g/Kg	Significant and dose-dependent anti-inflammatory activity	
			Writhing test	Aqueous extract	0.4, 0.28 g/kg 0.35, 0.5 g/Kg	↓number of mouse abdominal constrictions induced by acetic acid	
			Modification of VCAM-1 and ICAM1 expression by ELAISA	Neutral extract and isolated	Extract: 25, 50, 100, 200 μg/mL	significant dose-dependent ↓in vascular adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1) expression	
	<i>P. lentiscus</i> var. <i>chia</i>	Gum	U937 cell adhesion assay	phytosterol tirucalol	Tirucalol: 0.1, 1, 10, 100 μM	↓adhesion of U937 cells to TNF-α-stimulated human aortic endothelial cells	[98]
			Measurement of NFκB p65 phosphorylation by ELISA			↓phosphorylation of NFκB p65	
			Pyloric ligation, Aspirin-, phenylbutazone-, and reserpine-induced and cold-restraint stress ulcer in rat	Powder finely suspended in corn oil	An oral dose of 500 mg/kg	↓intensity of gastric mucosal damage in all models	[103]
	<i>P. lentiscus</i>	Resin	TNBS-induced colitis in rats	Powder in polyherbal formulation	50, 100, and 200 mg/kg of formula with 4% <i>P. lentiscus</i> resin	↓macroscopic and microscopic colonic damage; ↓TNF-α, IL-1β, MPO, and lipid peroxidation; not significantly increase in antioxidant power of colon	[106]
Effects on Gastrointestinal disorders	<i>P. lentiscus</i> var. <i>chia</i> .	Resin	3-week double-blind randomised placebo controlled study on patients with functional dyspepsia	Powder	350 mg TID	Improved the feeling of symptoms significantly	[104]
	<i>P. lentiscus</i> var. <i>chia</i> .	Resin	Dextran-sulfate sodium (DSS) model of colitis in mice	Powder	0.20 g/kg chow (0.02%) 2.0 g/kg chow (0.20%)	Delayed the onset and progression of acute colitis and ↓weight loss caused by the disease	[105]
	<i>P. lentiscus</i> var. <i>chia</i> .	Resin	4-week pilot study on 10 patients with Crohn's disease and 8 controls	Capsules of fine powder	2.22 g/day (6 caps/d, 0.37 g/cap)	↓Crohn's disease activity index and plasma inflammatory mediators such as C-reactive protein, interleukin-6 (IL-6) without any side effects; immunomodulatory effect by ↓ tumor necrosis factor-alpha (TNF-α) and ↑macrophage migration inhibitory factor	[107]

TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
	<i>P. lentiscus</i> var. <i>chia</i>	Resin	4-week pilot study on 10 patients with Crohn's disease and 8 controls	Capsules of fine powder	2.22 g/day (6 caps/d, 0.37 g/cap)	Immunomodulatory activity ↓TNF-α and ↑macrophage migration inhibitory factor (MIF) in these patients	[108]
Antidiabetic	<i>P. atlantica</i>	Leaf	In vitro and in vivo (normoglycemic and streptozocin-induced hyperglycemic rats)	Aqueous extract	2 mL plant extract equivalent to 200 mg of starting material	Significant inhibitory effect on α-amylase in vitro; no significant hypoglycemic activity in normoglycemic and hyperglycemic rats	[109]
			In vitro enzymatic starch digestion and rat model	Aqueous extract	1, 5, 10, 12.5, 25, 50, and 100 mg/mL 125, 250, and 500 mg/kg	In vitro: significant dose dependent dual inhibition of α-amylase and α-glucosidase comparable to acarbose In vivo: significant acute postprandial antihyperglycemic activity comparable to metformin and glipizide and improved glucose intolerance in oral starch tolerance test	[110]
	<i>P. lentiscus</i> var. <i>chia</i>	Resin	Human study	Powder diluted in 250 mL of water	0.7 g per day	Significantly decrease (3.1 mg/dL per month, $P = 0.003$ ) in serum glucose level among male subjects	[111]
	<i>P. lentiscus</i> var. <i>chia</i>	Resin	In vitro study on human colon cancer cells (HCT116)	Ethanol extract	ND	Inhibited proliferation and induced apoptosis of human colorectal tumor cells	[112]
			In vitro study on human leukemic cell line	Liquid and solid resin	0–200 μg/mL (solid mastic) or 0–2 (v/v)% of liquid mastic	The most cytotoxic effect against promyelocytic leukemia HL-60 among 13 human cell types; inhibition of natural apoptosis of oral polymorphonuclear leukocytes	[76]
			In vivo human colon cancer/immunodeficient mouse model	Hexane extract	200 mg/kg administered daily for 4 consecutive days (followed by 3 days without treatment)	Anticancer activity via its delay effect on the growth of colorectal tumors developed from HCT116 xenografted into mice	[8]
			Human cell line (androgen-responsive prostate cancer cell line) Human prostate cancer cell lines (LNCaP and DU-145), RT-PCR, and Western blotting were used to detect maspin expression	ND	2, 4, 6, 8, 10, and 12 μg/mL	Remarkable potency to decrease the expression and function of the androgen receptor in androgen-responsive prostate cancer cell line (LNCaP)	[154]
Antitumor	<i>P. lentiscus</i>	Resin	The human prostate cancer cell lines (PC-3), MTT assay, gene assay, RT-PCR, and Western blotting	ND	2, 4, 6, and 8 μg/mL	Increased maspin expression in LNCaP cells	[113]
			Lewis lung carcinoma cells	Essential oil	0.01% v/v	Inhibited proliferation and blocked the cell cycle progression in androgen-independent prostate cancer PC-3 cells by suppressing NF-κB activity and the NF-κB signal pathway	[114]
			Immunocompetent mice	Essential oil	45 mg/kg intraperitoneally, 3 times a week for 3 weeks	A time-dependent modification in the expression of 925 genes and phenomena in Lewis lung carcinoma cells by its antiproliferative, proapoptotic, and anti-inflammatory activities	[155]
	<i>P. atlantica</i> sub. <i>kurdica</i>	Fruit	Cells line and the in vivo chicken embryo CAM angiogenesis model	Essential oil	0.01–0.1% v/v	Significant inhibition on tumor growth without signs of toxicity related to apoptosis induction, reduced neovascularization, and inhibiting chemokine expression	[115]
						Antiproliferative and proapoptotic effect on K562 human leukemia cells; inhibited the release of vascular endothelial growth factor from K562 and B16 mouse melanoma cell; concentration-dependent inhibition of endothelial cell proliferation without affecting cell survival; significant decrease of microvessel formation	[116]



TABLE 3: Continued.

Pharmacological activity	Plant	Plant part	Assay	Extract/essential oil/isolated component	Dose or concentration	Observations	Ref.
			Rat liver medium-term carcinogenesis bioassay (Ho-test)	Powder in diet	0, 0.01, 0.1 and 1%	Promoted the preneoplastic lesions development in rat liver with increasing liver relative weight	[117]
			human colon carcinoma HT29 cells	Ethanol : H <sub>2</sub> O (70 : 30)	0.7 mg/mL	50% growth inhibition similar to 500 nM of doxorubicin	[119]
	<i>P. vera</i>	Resin	In vitro cytotoxic activity against human cell lines	Crud methanolic extract fractionated against petroleum ether, chloroform, and <i>n</i> -butanol	ND	Moderate cytotoxic effect against breast cancer cell line (MCF7), hepatocellular carcinoma cell line (HEPG2), cervix cancer cell line (HELA), and normal melanocytes (HFB4); <i>n</i> -hexane fraction showed strong cytotoxic effect (IC50: 3.15–4.17 µg/mL) against all of the tested cell lines, except for MCF7 (IC50: 13.5 µg/mL)	[120]
Effects on liver and serum biochemical parameters	<i>P. lentiscus</i>	Leaf	Rat model using Carbon tetrachloride	Aqueous extract	4 mL/kg (contained 1.946 g of solid matter)	↓bilirubin and activity of 3 enzymes including alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)	[121]
	<i>P. lentiscus</i> var. <i>chia</i>	Resin	Human model	Powder diluted in one glass (250 mL) of water	5 g	Hepatic fibrosis, an inflammatory response, mild cholestasis, and depletion of reduced glutathione associated with an increase in its oxidized form for five weeks administration in healthy rats; in thioacetamide-induced rat liver lesions, it aggravated the inflammatory, fibrotic, and glutathione depleting responses without affecting the extent of lipid peroxidation	[122]
	<i>P. vera</i>	Seeds oil	Rabbit model, mercury induced toxicity	<i>Pistacia</i> oil	5%	Serum total cholesterol, LDL, total cholesterol/HDL ratio, lipoprotein, apolipoprotein A-1, apolipoprotein B, AST, ALP, and gamma-GT were reduced in human subjects	[111]
Effects on atherosclerosis	<i>P. terebinthus</i>	Fruit	Rabbit model	Fruit	1 g/kg	Inhibited the development of hydropic degeneration and fatty changes in the liver and demonstrated hypolipidemic effect	[125]
	<i>P. vera</i>	Fruit	Rabbit model	Methanolic and cyclohexane extracts	Methanolic extract (1% v/w) cyclohexane extract (5% v/w)	Beneficial effects on HDL, LDL, and aortic intimal thickness. The methanolic extract additionally showed an antioxidant activity and remarkable decrease in aortic surface lesions	[123]
	<i>P. terebinthus</i>	Fruit	Rabbit model	Fruit	1 g/kg	Inhibited the development of the atherosclerotic lesions in the thoracic artery	[125]
Anticholinesterase activity	<i>P. atlantica</i>	leaf	TLC bioautography assay, Ellman's colorimetric method	Aqueous extract	5, 10, 15, 20, and 25 µg/mL	Restored intracellular antioxidant glutathione (GSH) levels and downregulated CD36 mRNA expression resulted in antioxidant and antiatherogenic effects	[126]
	<i>P. atlantica</i>	Leaf	Ellman's colorimetric method	Methanol and ethyl acetate extracts	0.1 mg/mL	Strong acetylcholinesterase (AChE) inhibition	[13]
	<i>P. terebinthus</i>	Fruit	Ellman's colorimetric method and the modified dopachrome method	Ethyl acetate and methanol extracts	25, 50, 100, and 200 µg/mL	Relatively weak AChE inhibitory activity	[127]
						No inhibitory activity against AChE and tyrosinase while selectively inhibited butyrylcholinesterase (BChE) at moderate levels (below 50%) at the tested concentrations	[85]

[32]. *P. vera* fruit revealed significant antioxidant activity similar to the synthetic antioxidant [81]. Lipophilic extract from *P. vera* nuts showed lower antioxidant potential than that of hydrophilic extract [82]. One survey showed *P. vera* skins had a better antioxidant activity compared to seeds by means of four different assays because of higher content of antioxidant phenolic compounds in skins [44]. Antioxidant activity has been also reported from other parts of *P. vera* [83].

In one study, the extract from *P. terebinthus* leaf had nearly 12-fold higher antioxidant capacity than those of BHA and ascorbic acid [84]. *P. terebinthus* fruits showed noticeable metal-chelation properties as compared to EDTA and high radical scavenging activity similar to the standards. Antioxidant activity of the fruits may be elevated by roasting process [85].

**4.2. Antimutagenic Activity.** Essential oil and different extracts from *P. lentiscus* leaves indicated significant inhibitory effect on mutagenicity in vitro [86, 87]. Gallic acid, digallic acid, and 1,2,3,4,6-pentagalloylglucose, polyphenols isolated from the fruits of *P. lentiscus*, induced an inhibitory activity against mutagenicity and genotoxicity in in vitro assays [47, 52].

**4.3. Antimicrobial and Antiviral Activities.** *Pistacia* species have demonstrated significant antibacterial activity against various Gram positive and Gram negative bacteria as shown in Table 3. Antimicrobial activity of *Pistacia lentiscus* resin, the essential oil and gum from *P. atlantica* var. *kurdica* and its major constituent  $\alpha$ -pinene and *P. vera* gum against *Helicobacter pylori* were recorded [15, 33]. A study indicated that antibacterial activity of *P. lentiscus* gum oil can be attributed to combination of several components rather than to one particular compound. Verbenone, R-terpineol, and linalool showed high antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* which is comparable to that of mastic oil itself [19]. *P. lentiscus* gum revealed selective antibacterial activity against *Porphyromonas gingivalis* and *Prevotella melaninogenica* and had antiplaque activity on teeth by inhibiting bacterial growth in saliva [76].

Significant antifungal activity was seen from essential oil of *P. lentiscus* leaf and gum, different extracts of *P. khinjuk* leaf, and essential oil of *P. vera* gum [15, 19, 38, 88]. Evaluating the effect of *P. vera* gum essential oil on growth of 13 bacteria and 3 yeasts demonstrated inhibitory effect on all of them except *Bacillus cereus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* and more effective yeasticide than nystatin. Carvacrol was found to be the most effective constituent [12, 15]. Lipophilic extracts from different parts of *P. vera* showed a little antibacterial activity and noticeable antifungal one against *C. albicans* and *C. parapsilosis*. Kernel and seed extracts showed significant antiviral activity [89].

Some active constituents of essential oil from the aerial parts of *P. khinjuk* responsible for its antibacterial and antifungal activity are  $\alpha$ -pinene,  $\beta$ -pinene, myrcene, beta-caryophyllene, Germacrene B, and Spathulenol [38].

Organic fraction of mastic water obtained during the steam distillation of resin from *Pistacia lentiscus* var. *chia*

indicated acceptable antifungal activity but moderate antibacterial effect. Among some of its major compounds, ( $\pm$ )-linalool and  $\alpha$ -terpineol had the highest antimicrobial effect [33].

Essential oil from leaf and gum of *P. atlantica* showed acceptable antibacterial and antifungal activities [90–92]. However, leaf ethanolic extract had no distinct antimicrobial activity [88].

A remarkable inhibitory activity of different extracts and essential oil from *P. lentiscus* leaves was observed against *Salmonella typhimurium*; additionally, essential oil showed significant inhibitory effects against *S. enteritidis* and *Staphylococcus aureus* [86, 87].

As reported by Adams et al. [55], the leaves and twigs of *P. atlantica* and its active substance 3-methoxycarpachromene showed antiprotozoal activity against *Plasmodium falciparum*. *P. atlantica* var. *kurdica* gum controlled cutaneous leishmaniasis in mice infected with *Leishmania major* [93]. Extract from *P. vera* branch had significant inhibitory activity against *Leishmania donovani* and leaf extract inhibited *Plasmodium falciparum* without cytotoxicity on mammalian cells [94].

**4.4. Anti-Inflammatory and Antinociceptive Activity.** Anti-inflammatory and antinociceptive activity of five mentioned *Pistacia* species have been shown in Table 3.

*P. terebinthus* gall showed anti-inflammatory activity in different in vivo models of acute and chronic inflammation [95]. Masticadienonic acid (26), masticadienolic acid (27), and morolic acid (28), three triterpene isolated from *P. terebinthus* gall, seem to be responsible for its anti-inflammatory activity [43]. Additionally, oleanonic acid (29) from the galls of *P. terebinthus*, reduced the production of leukotriene B4 from rat peritoneal leukocytes and showed antiedematous activity in mice [96]. Oleoresin and leaf extract from *P. vera* showed significant anti-inflammatory and antinociceptive activity [97].

Extract of the resin of *P. lentiscus* var. *Chia* and its isolated phytosterol tirucallol (31) showed anti-inflammatory activity on human aortic endothelial cells and had significant inhibitory activity on adhesion molecules expression in TNF- $\alpha$ -stimulated human aortic endothelial cells [98]. It was proposed that the anti-inflammatory effect of *P. lentiscus* var. *chia* gum may be related to inhibition of protein kinase C which leads to decrease in superoxide and H<sub>2</sub>O<sub>2</sub> production by NADPH oxidase [99].

**4.5. Effects on Gastrointestinal Disorders.** One of the most important traditional uses of gums from *Pistacia* species is for management of gastrointestinal disorders. Moreover, there are several scientific studies that confirm this property [100–102]. Resin of *P. lentiscus* significantly reduced the intensity of gastric mucosal damage induced by pyloric ligation, aspirin, phenylbutazone, reserpine, and restraint with cold stress via its antisecretory and cytoprotective activities [103]. In one double-blind placebo controlled trial, *P. lentiscus* gum improved the feeling of symptoms significantly in patients with functional dyspepsia [104]. Moreover, *Pistacia* species exerted significant antibacterial activity on *Helicobacter pylori*

[15, 33]. Supplementation with *P. lentiscus* oil in experimental model of colitis delayed the onset and progression of acute colitis and led to decrease weight loss caused by the disease [105]. A polyherbal formula that contains *P. lentiscus* gum caused significant decrease in colonic damage and biochemical markers related to pathophysiology of IBS in rat model of colitis [106]. Administration of *P. lentiscus* var. *chia* resin to patients with established mild to moderate active crohn's disease (CD) for 4 weeks caused significant reduction in CD activity index and plasma inflammatory mediators without any side effects and also as an immunomodulator resulted in significantly reduction in tumor necrosis factor-alpha (TNF- $\alpha$ ) and enhanced macrophage migration inhibitory factor in these patients [107, 108].

**4.6. Antidiabetic Activity.** Aqueous leaf extract from *P. atlantica* showed significant inhibitory effect on  $\alpha$ -amylase and  $\alpha$ -glucosidase in vitro [109, 110]. It demonstrated significant acute postprandial antihyperglycemic activity comparable to metformin and glipizide in starch-fed rats. It also improved glucose intolerance [110]. However, another study on this extract did not show significant hypoglycemic activity when tested in normoglycemic and streptozocin-induced hyperglycemic rats [109]. Administration of *P. lentiscus* var. *chia* gum to human subjects for 12 months caused significantly decrease in serum glucose level among male subjects. Serum glucose in women was not affected [111].

**4.7. Antitumor Activity.** Among mentioned species of *Pistacia*, *P. lentiscus* is the most investigated for antitumor activity (Table 3). *P. lentiscus* var. *chia* gum inhibited proliferation and induced apoptosis of human colorectal tumor cells in vitro [112]. The resin exerted the most cytotoxic effect against promyelocytic leukemia among 13 human cell types and also inhibited the natural apoptosis of oral polymorphonuclear leukocytes [76]. The gum demonstrated anticancer activity via delaying the growth of colorectal tumors developed from human colon cancer cells xenografted into mice [8]. It also increased maspin (a mammary serine protease inhibitor with tumor suppressive activity for prostate cancers) expression in responsive prostate cancer cells and inhibited cell proliferation and blocked the cell cycle progression [113, 114]. Essential oil of *P. lentiscus* demonstrated significant inhibition on tumor growth in immunocompetent mice without signs of toxicity, related to apoptosis induction, reduced neovascularization, and inhibiting chemokine expression [115]. In addition, it had antiproliferative and proapoptotic effect on human leukemia cells and inhibited the release of vascular endothelial growth factor from these cells [116]. Despite many reports on antitumor activities of *P. lentiscus*, one in vivo study showed that the high dose of *P. lentiscus* gum promoted the preneoplastic lesions development in rat liver with increasing liver relative weight which proposed that desirable anticarcinogenic effects of mastic could be obtained at relatively low doses [117]. In one recent study, the current data on the anticancer activities of gum, oil, and extracts of *P. lentiscus* L. and its major constituent, have

been reviewed comprehensively with special attention to the probable anticancer mechanisms [118].

The fruit extract of *P. atlantica* sub. *kurdica* showed growth inhibition in human colon carcinoma cells similar to Doxorubicin [119]. *P. vera* oleoresin demonstrated moderate cytotoxic effect against breast cancer cell line, hepatocellular carcinoma cell line, cervix cancer cell line, and normal melanocytes [120].

**4.8. Effects on Liver and Serum Biochemical Parameters.** *P. lentiscus* leaf demonstrated significant hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in rats by reducing the level of bilirubin and activity of liver enzymes [121]. However, another study reported hepatic fibrosis, mild cholestasis, and depletion of reduced glutathione by long-term administration of aqueous leaf extract in healthy rats [122]. Administration of *P. lentiscus* var. *chia* gum for 18 months in healthy volunteers caused reduction in liver enzymes and exerted hypolipidemic effect [111]. Extracts from *P. vera* fruits have shown beneficial effects on HDL and LDL level in rabbit model of atherosclerosis [123]. Positive changes in lipid profile were recorded after three-week use of *P. vera* nuts in patients with moderate hypercholesterolemia. The decrease in triglyceride and LDL levels was not significant [124]. *P. terebinthus* fruit demonstrated hypolipidemic effect in hypercholesterolemic rabbits [125].

**4.9. Effects on Atherosclerosis.** More over than the antihyperlipidemic activity that described above, *Pistacia* species exerts their antiatherosclerotic effects by direct activity on atherosclerotic lesions moreover than their antihyperlipidemic activity. Both methanolic and cyclohexane extracts from *P. vera* fruits have shown beneficial effects on HDL, LDL, and aortic intimal thickness in rabbit model of atherosclerosis. The methanolic extract additionally showed an antioxidant activity and remarkable decrease in aortic surface lesions [123]. *P. terebinthus* fruits inhibited the development of the atherosclerotic lesions in the thoracic artery [125]. *P. lentiscus* resin that downregulated CD36 mRNA expression (as the oxLDL receptor in macrophages that play a pivotal role in atherosclerotic foam cell formation) resulted in antiatherogenic effects [126].

**4.10. Anticholinesterase Activity.** Aqueous extracts from *P. atlantica* and *P. lentiscus* leaves showed strong acetylcholinesterase (AChE) inhibition [13]; additionally, both the methanol and ethyl acetate extracts of *P. atlantica* leaf showed relatively weak AChE inhibitory activity [127]. However, one study showed that ethyl acetate and methanol extracts of various commercially terebinth coffee brands (an oily brown-coloured powder produced from the dried and roasted fruits of *P. terebinthus*) and the unprocessed fruits of *P. terebinthus* did not have inhibitory activity against AChE and tyrosinase, while they selectively inhibited butyrylcholinesterase (BChE) at moderate levels [85].

## 5. Conclusion

In traditional Iranian medicine textbooks and papers, five species of *Pistacia* genus including *P. vera*, *P. lentiscus*, *P. terebinthus*, *P. atlantica*, and *P. khinjuk* had been introduced for treating the wide range of ailments. These species until now have been utilized in Iran by people for different nutritional and medicinal proposes. This review considered findings about phytochemical and pharmacological properties of these five species and presents comprehensive analysis of papers published since the year 2000. Ethnopharmacological data about these species may help us to know that many pharmacological aspects proposed nowadays for these species have been derived from traditional uses like antiseptic and antimicrobial, anti-inflammatory and antinociceptive, antihepatotoxic, and anticancer activities and their beneficial effects in gastrointestinal disorders. Furthermore, there are several pharmacological activities discussed in traditional medicine such as diuretic, lithontripic, anti-tussive, antirheumatic, antiasthmatic, antihypertensive, and aphrodisiac activities which are not supported by any current scientific documents, and so, they could be considered for investigation by researchers.

Phytochemical studies provided evidence for traditional applications of these species. With respect to phytochemical assays, triterpenes found in the resin and monoterpenes are the most abundant composition of the essential oil from different parts of these species. Essential oil constituents might be valuable chemotaxonomic marker to ascertain different *Pistacia* chemotypes. Considering the therapeutic effect of isolated components, it can be concluded that terpenoids including mono, di-, and triterpenoids are associated with anti-inflammatory and antimicrobial effects. High amount of natural phenols and flavonoids is related to potent antioxidant and anticancer activities.

Review on current researches about the genus *Pistacia* L. highlighting pharmacological studies on crude plant parts, extracts, and some pure metabolites has provided scientific evidence for traditional uses and has revealed this genus to be a valuable source for medicinally important molecules.

So many studies were carried out on antioxidant activity of this genus considering their flavonoids, anthocyanins, and other phenolic compounds as preventive factors against cancer and cardiovascular diseases. *P. lentiscus* is the most studied species for antioxidant effects followed by *P. atlantica*, *P. vera*, *P. terebinthus* and *P. khinjuk*.

Most of the studies showed antimicrobial activity of these species especially *P. lentiscus* on a wide range of microorganisms including Gram-positive and -negative, aerobic and anaerobic bacteria, viruses and fungi. The findings indicated that  $\alpha$ -pinene, verbenone, R-terpineol, linalool, carvacrol and flavones are major compounds related to antibacterial activity.

## Abbreviations

ABTS: 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)  
 ALP: Alkaline phosphatase  
 ALT: Alanine aminotransferase

AST: Aspartate aminotransferase  
 B(a)p: Benzo(a)pyrene  
 BHA: Butylated hydroxyanisole  
 BHT: Butylated hydroxytoluene  
 DMPD: N,N-dimethyl-p-phenyldiamine  
 DPPH: 2,2-Diphenyl-1-picrylhydrazyl  
 EC50: Half maximal effective concentration  
 EDTA: Ethylenediaminetetraacetic acid  
 EPP: Ethyl phenylpropionate  
 FRAP: Ferric reducing antioxidant power  
 Gamma-GT: Gamma-glutamyl transpeptidase  
 IC50: The half maximal inhibitory concentration  
 LOX: Lipoxygenase  
 MBC: Minimum Bactericidal Concentration  
 MDA: Malonaldehyde  
 MIC: Minimum inhibitory Concentration  
 NF- $\kappa$ B: Nuclear factor kappa-light-chain-enhancer of activated B cells  
 OxLDL: Oxidized low density lipoprotein  
 PLA2: Phospholipase A2  
 SGOT: Serum glutamic oxaloacetic transaminase  
 SGPT: Serum glutamic-pyruvic transaminase  
 SOD: Superoxide dismutase  
 TBARS: Thiobarbituric acid reactive substances  
 TBHQ: Tertiary Butyl hydroquinone  
 TPA: 12-O-Tetradecanoylphorbol-13-acetate.

## Conflict of Interests

The authors declare that they have no conflict of interests.

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