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Review

Pistacia lentiscus: phytochemistry and anti-diabetic properties

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Abstract: *Pistacia lentiscus* L. (*P. lentiscus*) is an evergreen shrub (Anacardiaceae family) primarily found in the Mediterranean region. The plant has been thoroughly characterized resulting to contain a high concentration of bioactive compounds as flavonoids and phenolics. Moreover, *P. lentiscus* reveal to possess a great nutritional and industrial importance because of its variety of biological activities including antibacterial, anti-inflammatory, anti-atherogenic and antioxidant properties. Many of its beneficial health properties and applications date back to antiquity, and the European Medicines Agency officially acknowledged it as an herbal medicinal product. Indeed, it is widely employed in conventional medicine to treat several diseases, including type 2 diabetes (T2D). On this basis, this review aims to summarize and describe the chemical composition of different parts of the plant and highlight the potential of *P. lentiscus* focusing on its antidiabetic activities. The plant kingdom is drawing increasing attention, because of its complexity of natural molecules, in the research of novel bioactive compounds for drugs development. In this context, *P. lentiscus* demonstrated several *in vitro* and *in vivo* antidiabetic effects, acting upon many therapeutic T2D targets. Therefore, the information available in this review highlighted the multitarget effects of *P.lentiscus* and its great potential in T2D treatment.

Keywords: *Pistacia lentiscus*; Chios mastic gum; diabetes; therapeutic target; hypoglycaemic effect; hypolipidemic effect

1. Introduction

Pistacia lentiscus L. is an evergreen shrub belonging to the Anacardiaceae family, mainly distributed in Mediterranean region. It is commonly used in traditional medicine for treatment of several diseases including diabetes [1–3]. This plant is also known as lentisk or mastic tree. The latter name derives from the presence of an aromatic resin (mastic) which can be obtained from *P. lentiscus* trunk and branches. Chios mastic gum is exclusively produced by the mastic tree grown on the Greek island of Chios, a situated in the northern Aegean Sea. Many of its beneficial properties and uses had already been attributed in the antiquity [4], and in 2015 it was recognized by the European Medicines Agency (EMA) as an herbal medicinal product with therapeutical indication for mild dyspeptic disorders and skin inflammation as well as healing of minor wounds [5,6] Over the last years, mastic gum has been used as a spice in food industry, as a food ingredient and one of the main uses is to produce a natural chewing gum. The therapeutic potential of mastic gum in medicinal field has also been described. Anti-inflammatory action has been reported probably being performed via the inhibition of pro-inflammatory substances production. Moreover, antioxidant, anti-atherogenic, anticancer, and antibacterial properties have been reported [6]. Because of the resin's chemical complexity, it's difficult to understand which bioactive compounds are responsible for these activities, even if some of them were attributed to triterpenes and volatile compounds[5]. The other parts of the plant were extensively investigated and

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also resulted in high content of bioactive compounds as phenolic or flavonoids showing several biological activities such as antioxidant, antimicrobial, hepatoprotective and antimutagenic activities [3,7].

In this contest, the present review aims to summarize and focus on the antidiabetic activity of *Pistacia lentiscus* highlighting the great potential of this plant for diabetes treatment.

Diabetes mellitus (DM) is a progressive metabolic disease characterized by abnormal blood glucose levels[8]. Diabetes is becoming more common worldwide as a result of unhealthy lifestyle choices, and by 2030, there will be 578 million cases of the disease[9]. Furthermore, the incidence of diabetes should be regarded as significantly higher, since 45% of individuals have undiagnosed diabetes.

Pancreatic β-cells secrete the peptide hormone insulin, which is essential for controlling blood glucose levels and energy metabolism. Numerous cellular processes, including the uptake and transport of glucose, the synthesis of glycogen, the synthesis of fatty acids, and the synthesis of proteins, depend on it. Hyperglycemia eventually results from impaired normal glucose homeostasis caused by either insufficient insulin production or insulin resistance [10]. Chronic hyperglycemia has been linked to major long-term consequences such as kidney failure, cardiovascular disease, and nerve damage [11].
Diabetes could be divided into type 1 and type 2 diabetes. The most prevalent metabolic diseases affecting children is type 1 diabetes (T1D), sometimes referred as insulin-dependent diabetes [12]. Pancreatic β-cells are destroyed by the immune system through T-cell mediation in the pathophysiology of T1D. This ultimately causes the body to secrete less insulin, which causes the beginning of the disease [13].

Instead, type 2 diabetes (T2D) accounts for 90–95% of all instances of the disease and it represents the most common type [14]. Insulin resistance and decreased insulin production work together to create this type of diabetes[15]. The failure of skeletal muscle cells to absorb glucose and the increased synthesis of glucose in the liver are two examples of how the target tissues are insensitive to insulin [16]. Obesity, physical inactivity, and vitamin D insufficiency are the main risk factors linked to the development of T2D [17].

Insulin injections are commonly used as a form of treatment for T1D, while oral drugs in conjunction with lifestyle modifications are utilized to manage T2D [18]. Non-insulin medications obstruct the absorption of glucose, reduce hepatic gluconeogenesis, and prevent the kidneys from reabsorbing glucose. α-Glucosidase inhibitors, metformin, and sodium-glucose co-transporter-2 inhibitors are a few examples of popular anti-diabetic medications that support the above-mentioned effects [19]. However, even though these medications have a significant role in lowering blood glucose levels, side effects are unavoidable.

The plant kingdom is attracting increasing interest in finding new bioactive compounds for the development of drugs, also due to the intrinsic complexity of natural compounds [20]. Over 800 plants have been reported to possess antidiabetic properties, showing less side effect if compared with synthetic drugs and different bioactive compounds with different biological activities have been described [21–24].

P. lentiscus showed to possess several *in vitro* and *in vivo* antidiabetic properties, exerting activities toward different therapeutic T2D targets. Here, chemical composition of different parts of the plant together with *P. lentiscus* biological activities are summarized and described.

2. Chemical constituents

From the literature review, a total of 180 compounds were identified in *Pistacia lentiscus*, including essential oil constituents, monoterpenoids, sesquiterpenoids, triterpenoids, phenolic compounds, flavonoids, fatty acids, steroids, tannins, and miscellaneous compounds. Phytochemicals were isolated from various parts of the plants, including leaves, fruits, resin, aerial parts, barks. According to the literature, the most common

methods used to identify phytochemicals from the genus Pistacia, notably from its essential oils, were high-performance liquid chromatography (HPLC) and the gas chromatography-mass spectroscopy (GC-MS). These techniques allowed to obtain qualitative and quantitative information on the biochemical constitution of *Pistacia lentiscus*. Terpenoids constitute the major chemical group comprising approximately the 54% of the total chemical constituents following by phenolic and flavonoids compounds (13-15%), fatty acids, steroids, tannins (2-5%) and several miscellaneous compounds (5%) (Figure 1). Another category is the volatile compounds included in the essential oil and mastic water, two products obtained after the distillation process of mastic gum.

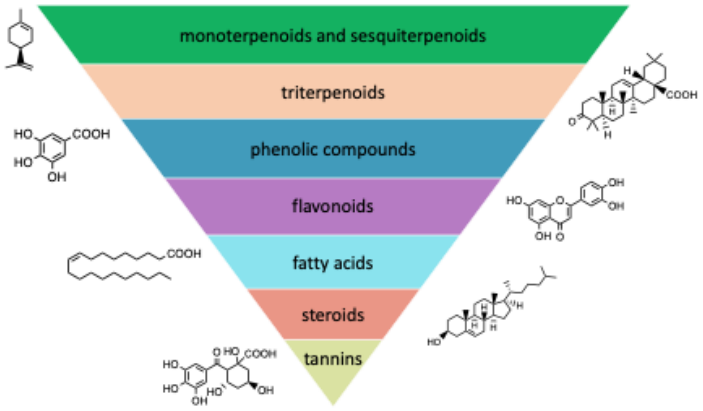


Figure 1. Chemical composition of *Pistacia Lentiscus*

Several phenolic acids were detected, among which gallic acid (**107**) was recovered by several authors [1,25–28]. Quinic acid derivatives and galloyl derivatives such as 3,5-*O*-digalloyl quinic acid (**163**), 3-galloyl quinic acid (**165**) and 3,4,5-tri-*O*-galloyl quinic acid (**164**), 5-galloyl quinic acid (**166**) and 1,5-digalloyl quinic acid (**170**) were detected [1,26].

Further studies also reported the presence of vanillic acid (**108**) [27], *p*-coumaric acid (**113**) [27], *trans*-cinnamic acid (**112**) [25], caffeic acid (**114**) [25,27], ferulic acid (**115**) [29] and tannic acid (**169**) [25]. Flavonol glycosides were found to be the most abundant class of flavonoids in the leaves and fruits of *Pistacia lentiscus*. Myricetin-3-*O*-rhamnoside (**135**) [1,26] was the predominant flavonol glycoside followed by myricetin-3-*O*-glucoside (**134**) [1,26] and quercetin-3-*O*-rhamnoside (**136**)[1,28]. Myricetin derivatives account for 20% of the total amount of polyphenols in *P. lentiscus* leaves [1]. Luteolin (**122**) and apigenin (**126**), belonging to the class of flavones, were observed in high concentration in both leaves and fruit extracts [1,28]. Mehenni et al. [28] found luteolin to be the second most abundant polyphenol in fruit. Flavonoid namely, delphinidin-3-*O*-glucoside (**132**) and cyanidin-3-*O*-arabinoside (**133**) were identified in berries and leaves [1].

Variable levels of total phenolic contents, flavonoids, and condensed tannins were found in all parts of *P. lentiscus*. The concentration of secondary metabolites changes significantly according to geographical origin, phenological stages, parts of plant used, cultivation sites, extraction solvents used. Recent phytochemical analyses have shown that all the parts (leaf, stem, fruit, and root) of *P. lentiscus* are rich in bioactive phenolic components. For example, a study on Algerian mastic tree showed that total phenolic mass fraction in leaves as gallic acid equivalents on dry matter basis (216.28 ± 20.62 mg/g) was significantly higher than that in stems (121.39 ± 3.35 mg/g), fruits (103.34 ± 2.32 mg/g) and roots (30.18 ± 1.29 mg/g). Among the phenolic compounds, the most abundant were the flavonoids myricetin glycoside (**134**), catechin (**124**), β-glucogallin (**162**), and gallic (**107**) and 5-*O*-galloylquinic acids (**161**)[2].

A study conducted by Mehenni et al.[28] asserts that the highest amounts of polyphenols were recorded in the aqueous chloroform extracts of both leaves and fruits, followed by in ethanolic and aqueous ethyl acetate extracts. More specifically, the total amounts of phenolics and flavonoids of leaf crude extracts (517.512 ± 5.53 mg catechin Eq/g and 108.67 ± 0.5 mg rutin Eq/g, respectively) were significantly ($p < 0.01$) higher than those found in fruit crude extracts (254.9 ± 5.04 mg catechin Eq/g and 3.49 ± 1.19 mg rutin Eq/g, respectively).

Aerial parts (leaves and fruits) of fresh *P. lentiscus* collected in different area of Sardinia showed that in the leaves are present a large number of polyphenols, in particular members of myricetin (**127**, **135**, **136**, **142**, **143**) and quercetin (**128**, **129**, **140**, **141**). In contrast, phenolic acids predominate in fruits (**107**, **163**, **165**, **166**, **170**)[26].

According to Belhachat[30]and Yosr[31], the total phenolic content varied from 17 mg gallic acid equivalent (GAE)/g dry matter (DM) to 955 mg GAE/g DM in the *P. lentiscus* extracts and among the same leaves extract, changes also depended on sex (100.8 vs 150.7 mg GAE/g DM in female and male respectively) and phenological stages (178.5 vs 87 mg GAE/g DM in dormancy period and late fruiting stage respectively)[31].

Considering the fatty oil extracted from fruits of *P. Lentiscus* (PLFO), Djerrou et al. [32] reported that it showed a good ratio (0.86) of polyunsaturated fatty acid/saturated fatty acid. The fatty acid composition consists of three dominant fatty acids: oleic acid (**150**) (monounsaturated) at 54.4%, palmitic acid (**154**) (saturated) at 22.5% and linoleic acid (**152**) (polyunsaturated) at 19.8%. The oil also contains sterols (**157**-**160**), tocopherol (**171**), carotenoids and chlorophyll.

Furthermore, the oil is a rich source of phenolic compounds, with about 40 molecules identified, as gallic acid (**107**), tyrosol (**104**), vanillic acid (**108**) and flavonoids as kaempferol (**123**) and quercetin (**125**) [33]. The total phenolic content (TPC) and total flavonoid content (TFC) for PLFO determined to be 25.19 ± 0.67 μg GAE/mg and 20.90 ± 4.41 μgquercitin equivalent (QE)/mg of PLFO, respectively. In the case of the unsaponifiable fraction (USM), the quantity of TPC and TFC values were found to be 18.70 ± 2.89 μg GAE/mg and 12.5 ± 2.65 μg QE/mg of USM, respectively[33].

El Omari et al. [34]revelated that the mail compounds of *P. Lentiscus* essential oil extracted from fruits are α-pinene (**1**) (20.46%) and limonene (**3**,**10**) (18.26%), consequently both compounds were individually tested for the biological effects.

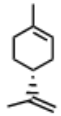
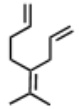
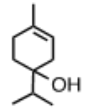
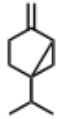
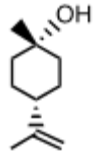
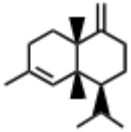
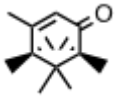
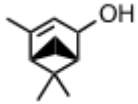
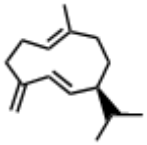
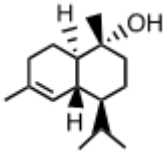
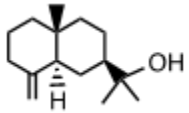
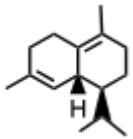
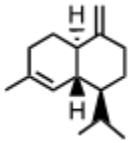
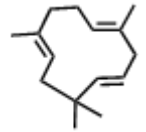
Kartalis et al.[35] described the effects of Chios mastic gum (CMG) on cholesterol and glucose. CMG's main components are an insoluble polymer (25%) and a triterpenic fraction (67%), which is further subclassified as acidic (39%) and neutral (28%) fractions. The acidic fraction main components are the masticadienonic acid (**50**) (30%), isomasticadienonic acid (**49**) (30%), oleanonic acid (**51**) (15%) and moronic acid (**47**) (10%). The neutral fraction's main components include butyspermol (**55**), tirucallol (**63**), oleanolic aldehyde (**57**), and betulonal (**61**). Another monoterpenic constituent of CMG, camphene (**7**), seems to possess promising hypolipidemic activity. Antioxidant effects of Chios mastic, that may result in reducing LDL cholesterol oxidation, could be attributed to the resin's remarkable concentration of various polyphenols.

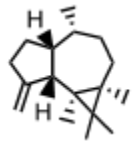
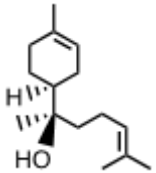
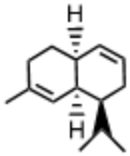
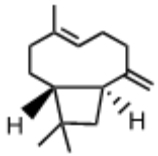
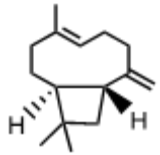
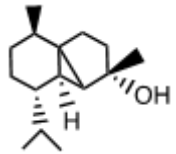
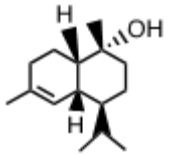
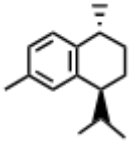
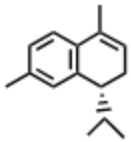
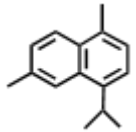
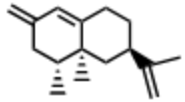
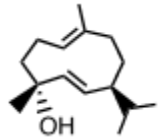
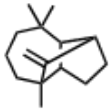
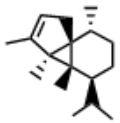
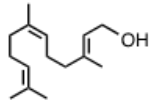
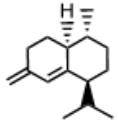
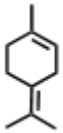
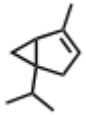
However, any discrepancies in secondary metabolites concentrations may be due to the collection period as well as soil conditions.

All the compounds identified in *P. lentiscus*, divided by class of molecules, are summarized below in Table 1.

The overall analysis of the chemical composition showed that *P. lentiscus* contains several bioactive molecules. The antidiabetic activities of extracts and/or single compounds from *P. lentiscus* are in depth described in the following section.

Table 1. Chemical compounds identified or isolated from *Pistacia lentiscus*.

Monoterpenoids and sesquiterpenoids					
					
α-P*inene*(1)	β-P*inene* (2)	R-Limonene (3)	β-Mircene (4)	Terpinen-4-ol (5)	Sabinene (6)
					
Camphene (7)	*p*-Cymene (8)	β-Phellandrene (9)	S-Limonene (10)	*trans*-β-Terpineol (11)	α-Terpineol(12)
					
γ-Terpinene (13)	γ-Muurolene (14)	Verbenone (15)	*trans*-Verbenol (16)	*trans*-Pinocarveol (17)	2-Carene (18)
					
Germacrene D (19)	α-Cadinol (20)	β-Eudesmol (21)	δ-Cadinene (22)	γ-Cadinene (23)	α-Humulene (24)

					
β-Gurjunene (25)	α-Bisabolol (26)	α-Amorphene (27)	(-)-β-Caryophyllene (28)	(+)-β-Caryophyllene (29)	Cubebol (30)
					
Cedreanol (31)	*trans*-Calamenene (32)	α-Calacorene (33)	Cadalene (34)	Nootkatone (35)	Germacrene-D-4-ol (36)
					
Longifolene (37)	α-Cubebene (38)	Linalool (39)	Farnesol (40)	Epi-bicyclosesquiphellandrene (41)	
					
α-Terpinolene (42)	α-Thujene (43)				

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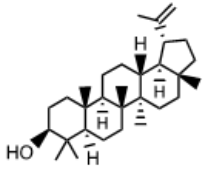
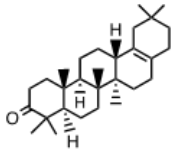
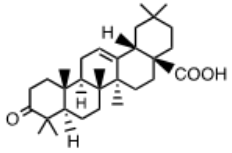
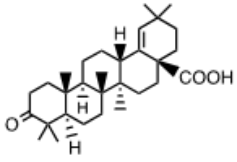
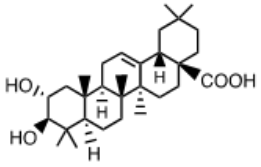
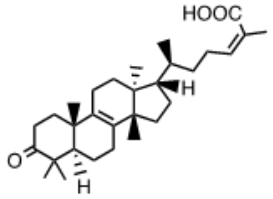
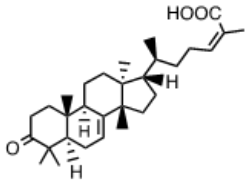
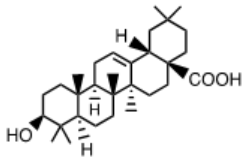
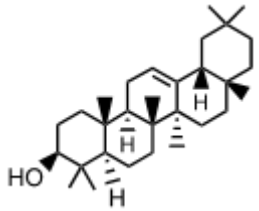
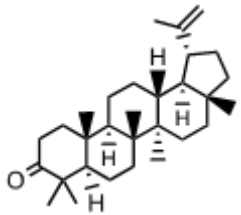
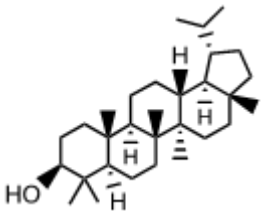
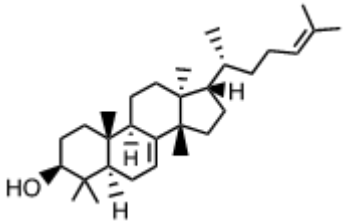
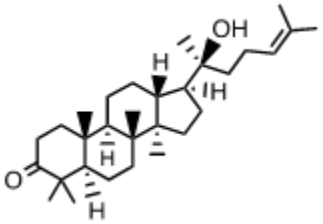
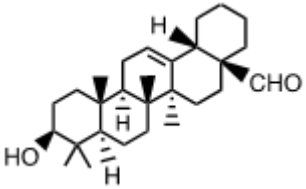
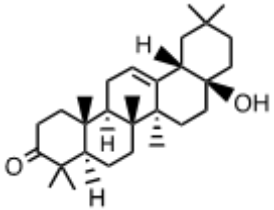
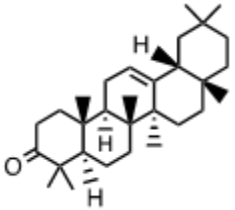
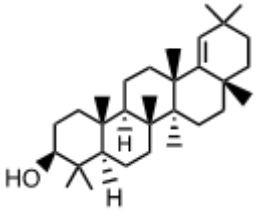
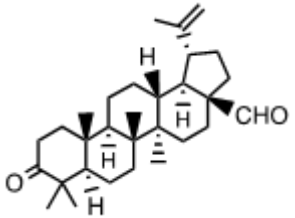
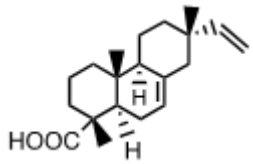
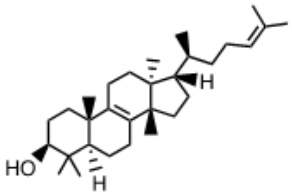
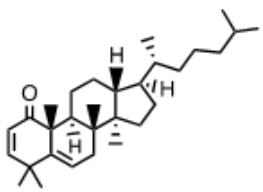
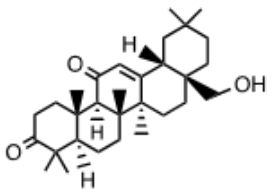
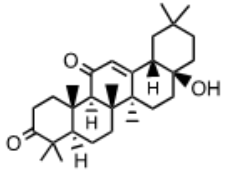
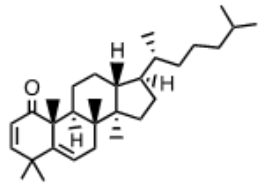
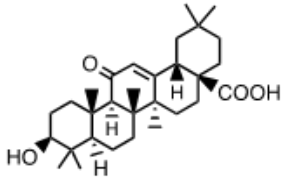
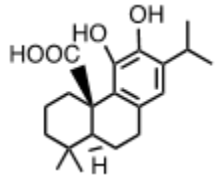
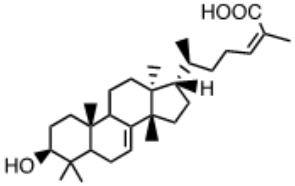
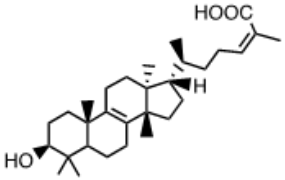
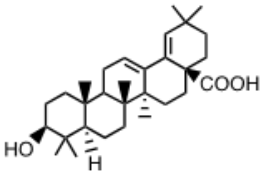
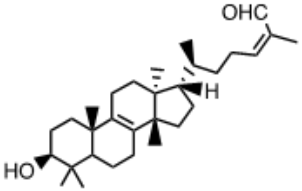
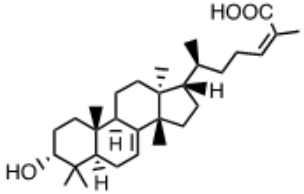
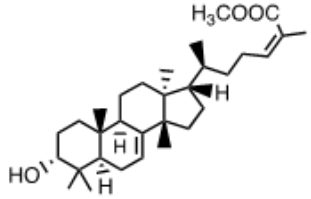
Triterpenoids				
				

Lupeol (44)	28-Norolean-17-en-3-one (45)	Oleanonic acid (46)	Moronic acid (47)	Maslinic acid (48)
				
24-Z-Isomasticadienoic acid (49)		24-Z-Masticadienoic acid (50)		Oleanolic acid (51)
				
β-Amyrin (52)	Lupenone (53)	Lupanol (54)	Butyrospermol (55)	Dipterocarpol (56)
				
Oleanolic aldehyde (57)	28-Hydroxy-β-Amyrone (58)	β-Amyrone (59)	Germanicol (60)	Betulonal (61)
				
Isopimaric acid (62)	Tirucallol (63)	Dammaradienone (64)	Krukovine A (65)	3,11-Dioxo-28-norolean-12-en-17-ol (66)

		
3,7,11-Trioxo-8,24(Z)-tirucalladien-26-oic acid (67)	3-β-Hydroxy-11-oxo-olean-12-en-28-oic acid (68)	Carnosic acid (91)
		
24-Z-Masticadienolic acid (92)	24-Z-Isomasticadienoilic acid (93)	Olean-12,18-dien-3-olic acid (94)
		
Isomasticadienolic aldehyde (95)	3-Epimasticadienolic acid (96)	Methyl 3-epimasticadienolate (97)

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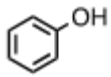
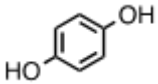
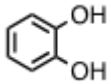
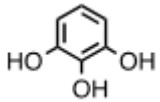
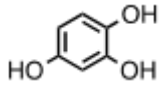
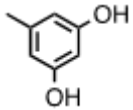
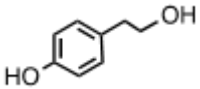
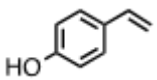
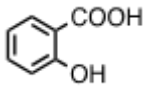
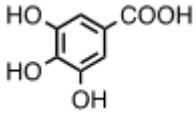
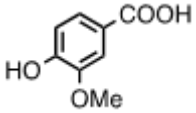
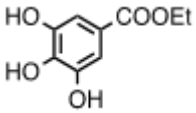
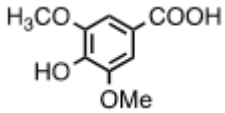
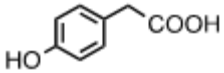
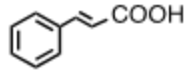
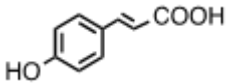
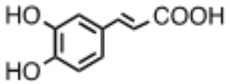
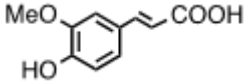
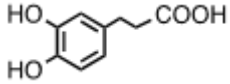
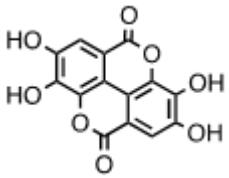
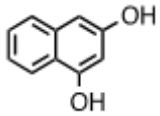
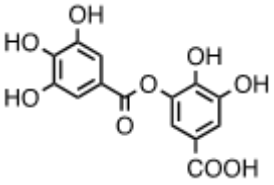
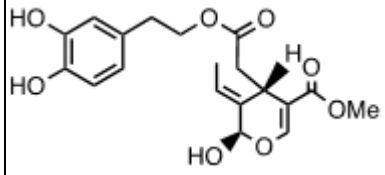
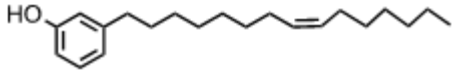
PhenolicCompounds				
				
Phenol (98)	Hydroquinone(99)	Catechol(100)	1,2,3-Benzenetrienol (101)	Hydroxyquinol(102)
				

Orcinol (103)	Tyrosol (104)	4-Vynilphenol (105)	Salicilic acid (106)	Gallic acid (107)
				
Vanillic acid (108)	Ethyl gallate (109)	Syring acid (110)	4-Hydroxyphenylacetic acid (111)	*trans*-Cinnamic acid (112)
				
p-Coumaric acid (113)	Caffeic acid (114)	Ferulic acid (115)	3,4-Dihydroxyhydro-cinnamic acid (116)	Ellagic acid (117)
				
Naphtoresorcinol (118)	Digallic acid (119)	Oleuropeinaglycon (120)	(Z)-3-(Pentadec-8-en-1-yl)phenol(121)	

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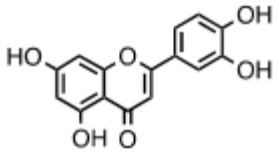
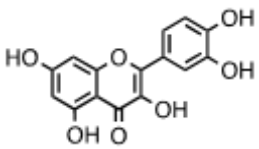
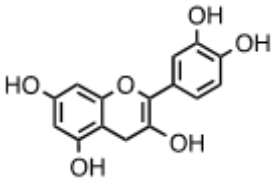
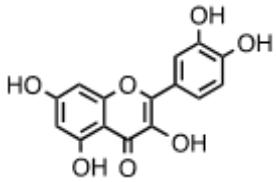
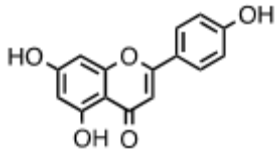
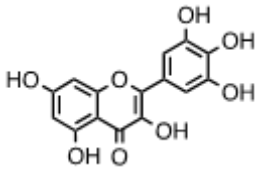
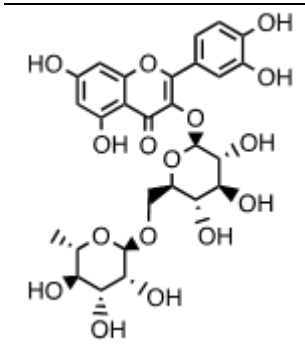
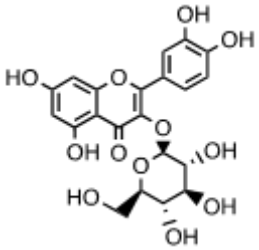
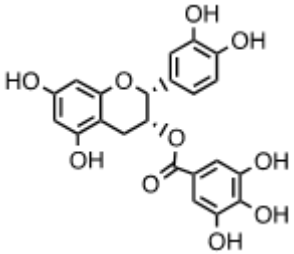
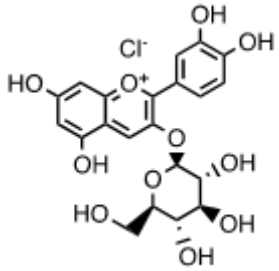
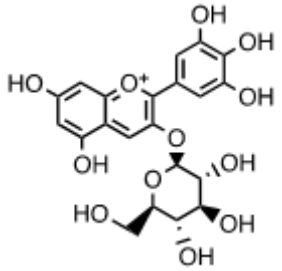
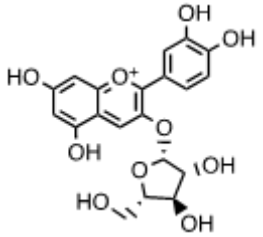
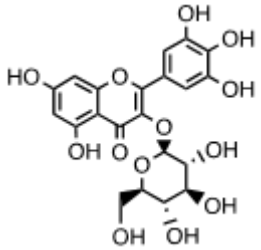
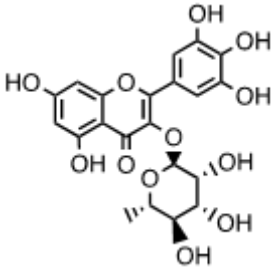
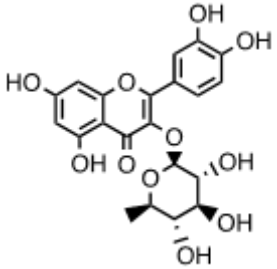
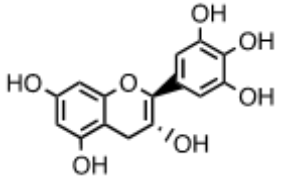
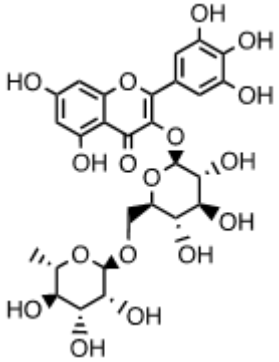
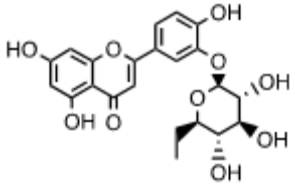
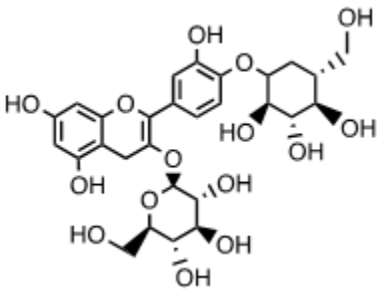
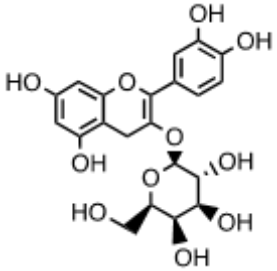
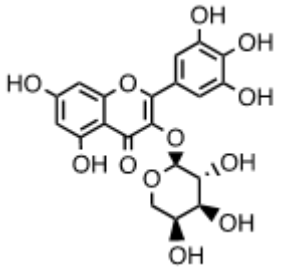
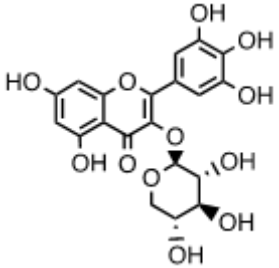
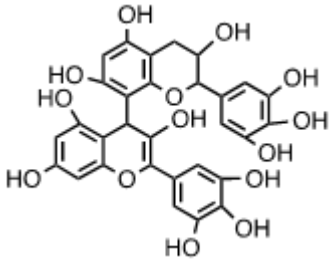
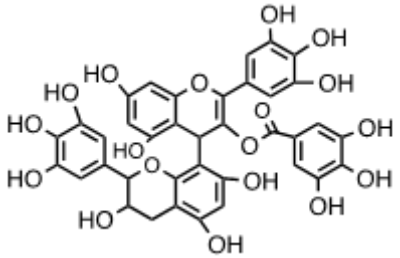
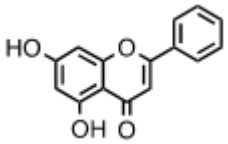
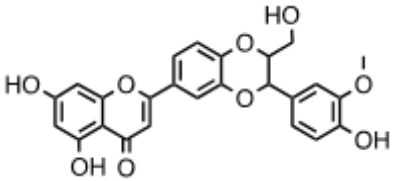
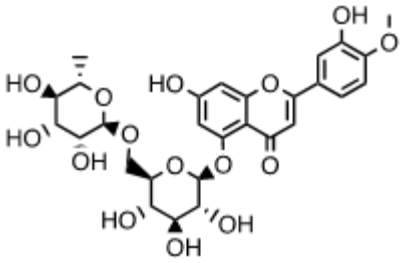
Flavonoids					
					
Luteolin (122)	Kaempferol (123)	Catechin (124)	Quercetin (125)	Apigenin (126)	Myricetin (127)

					
Rutin (128)	Quercetin 3-*O*-glucoside (129)	Epicatechin- 3-gallate (130)	Cyanidin 3-*O*-glucoside (131)	Delphinidin 3-*O*-glucoside (132)	Cyanidin 3-*O*-arabinoside (133)
					
Myricetin 3-*O*-glucoside (134)	Myricetin 3-*O*-rhamnoside (135)	Quercetin 3-*O*-rhamnoside (136)	D-Gallocatechin (137)		
					
Myricetin 3-*O*-rutinoside (138)	Luteolin-3′-*O*-glucoside (139)	Quercetin 3,4′-Diglucoside (140)	Quercetin-3-*O*-Galactoside (141)		

			
Myricetin 3-*O*-arabinopyranoside (142)	Myricetin 3-*O*-xylopyranoside (143)	Epigallocatechin(4a>8)epigallocatechin (144)	(Epi)gallocatechin-3′-*O*-galloyl-(epi)gallocatechin (145)
			
Chrysin (146)	Silymarin (147)	Deosmin (148)	

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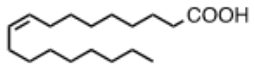
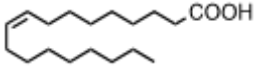
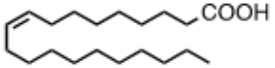
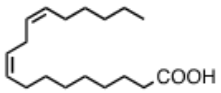
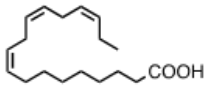
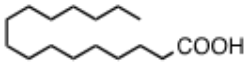
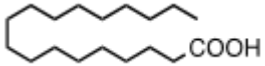
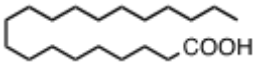
Fatty acids			
			
Palmitoleic acid (149)	Oleic acid (150)	Gadoleic acid (151)	Linoleic acid (152)
			

Linolenic acid (153)	Palmitic acid (154)	Stearic acid *(155)*	Arachidic acid (156)

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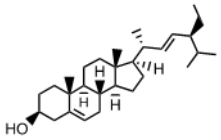
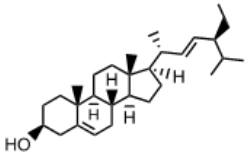
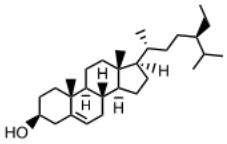
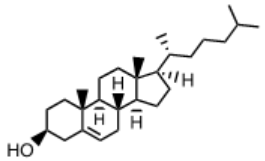
Steroids			
			
Campesterol (157)	Stigmasterol (158)	β-Sitosterol (159)	Cholesterol (160)

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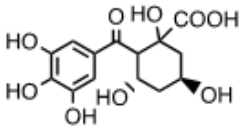
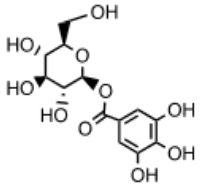
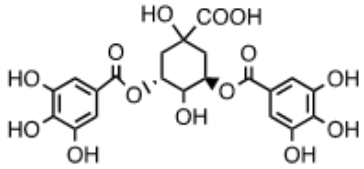
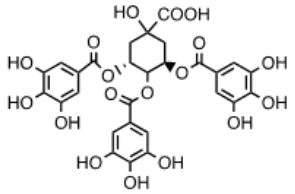
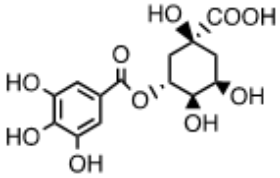
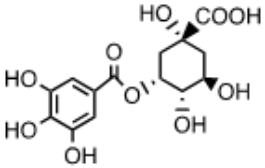
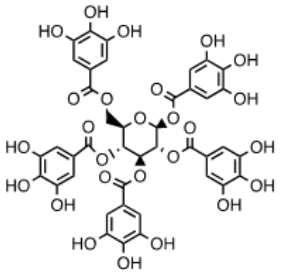
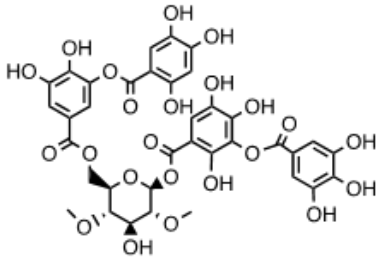
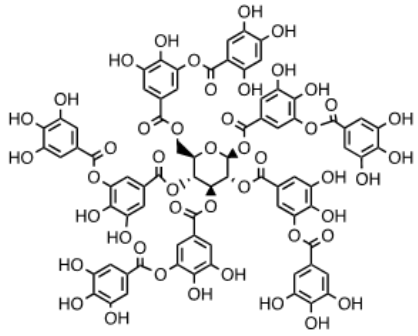
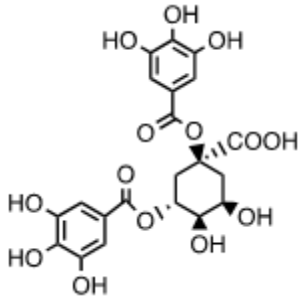
Tannins			
			
Galloylquinic acid (161)	β-Glucogallin (162)	3,5-Digalloyl quinic acid (163)	3,4,5-Trigalloyl quinic acid (164)
			
3-Galloyl quinicacid (165)	5-Galloyl quinicacid (166)	1,2,3,4,6-Pentagalloyl glucose (167)	3,5-Dimethoxy-4-hydroxy-tannic acid (168)

	
Tannic acid(169)	1,5-Digalloyl quinic acid (170)

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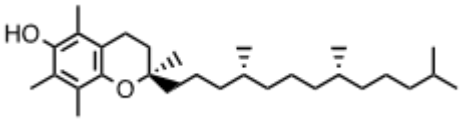
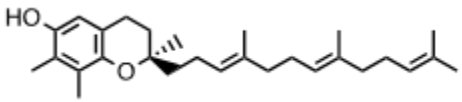
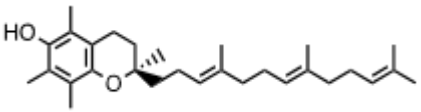
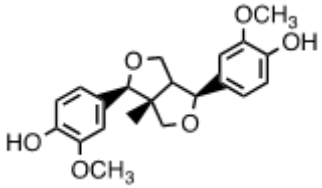
Miscellaneous compounds			
			
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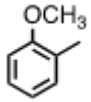
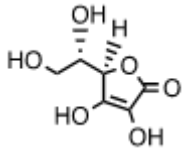
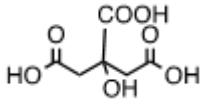
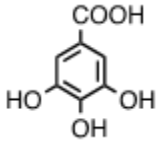
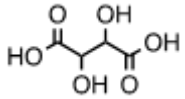
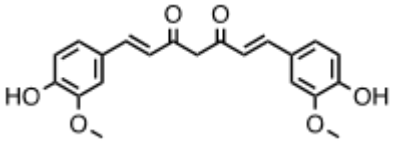
			
o-Methylanisol (175)	Ascorbic acid (176)	Citric acid (177)	Pyrogallic acid (178)
			
Tartaric acid (179)	Curcumin (180)		

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3. Anti-diabetic properties

3.1. In vitro experiments

3.1.1. α-Glucosidase and α-amylase inhibition

α-Glucosidase (E.C. 3.2.1.20) and α-amylase (E.C.3.2.1.1) belong to the enzyme targets in the T2D treatment. Inhibition of these enzymes result in a decrease in glucose production and absorption after a meal. In fact, these digestive enzymes first act in the mouth with the activity of the salivary α-amylase, produced by salivary glands. Then, the digestion carries on in the lumen of the small intestine with the endoglycosidase activity of the pancreatic α-amylase, producing short oligosaccharides which can by hydrolysed by α-glucosidase. α-Glucosidase, present in the brush border of the small intestine, produces therefore free glucose that can be absorbed and addressed into the blood. Thus, in diabetic patients, one strategy is to inhibit these enzymes in order to prevent the post-prandial hyperglycemia.

Inhibitory effect toward these enzymes by *P. lentiscus* has been reported.

Foddai et al.[26] reported the inhibition of enzymatic starch digestion by aqueous extract from *P. lentiscus* leaves and fruits. A dose-dependent reduction in glucose release from starch hydrolysis was observed and the IC_{50} values from leaves and fruits extracts resulted to be 65.3 ± 7.4 μg/mL and 1.4 ± 0.2 μg/mL, respectively. The inhibition of α-glucosidase and α-amylase activity separately was also investigated. α-Amylase inhibition exerted by ethanolic extract from leaves and fruits was reported by Mehenni et al [28]. Both extracts showed inhibition but less effective than that of acarbose, the standard inhibitor, being leaves extract the more active with an IC_{50} value of 87.5 μg/mL, lower than that of fruit extract (IC_{50} of 144.29 μg/mL).

These results were also confirmed by Tebbi et al.[25], that studied the inhibitory effect of *Pistacia lentiscus* L. black fruits, extracted by choline chloride-acetic acid (ChCl-Acet) deep eutectic solvent (DES) against α-amylase and founded that the extract showed a good inhibitory activity on α-amylase with a percentage of 64.03 ±1.21% at 25 μg/mL.

Black fruits were also evaluated by Hamdi et al. [33]for their ability to inhibit α-amylase and α-glucosidase. *Pistacia lentiscus* fatty oil (PLFO) of the extract and the unsaponifiable matter (USM) were separated and examined for the above mentioned anti-diabetic activities. PLFO displayed a low inhibitory effect on α-amylase (IC_{50}> 400 μg/mL), although USM demonstrated much greater inhibitory activity, with a IC_{50} value of 180.93 μg/mL, 20 times more effective than the standard molecule, acarbose (IC_{50} of 3650.93 μg/mL). This significant inhibition of α-amylase enzyme by the unsaponifiable matter emphasizes the significance of its isolation from the oil. As regard α-glucosidase inhibitory activity, both PLFO and USM extracts exhibited good inhibitory activity (IC_{50} values of 136.47 and 155.77 μg/mL, respectively) in comparison with acarbose (IC_{50} of 275.43 μg/mL). These results indicate that the inhibition of α-glucosidase could be attributed to USM but there was no change in the inhibitory power as a result of its separation from the oil.

According to Sehaki et al. [1] aqueous lentisk extracts from leaves, stem barks and fruits presented different percentages of inhibition against α-glucosidase at a concentration of 10 μg/mL, harvested from the two locations in Tizi-Ouzou (i.e., littoral and mountain). The stem bark extracts were the most effective, with average values of 84.7 ± 5.9% ($IC_{50}$of 5.8 ± 0.4μg/mL) and 69.9 ± 19.9% ($IC_{50}$of 7.9 ±3.3μg/mL) at the littoral and mountain, respectively, followed by leaves and finally the fruit extracts, that showed the lower inhibitory activity (13.6 ± 6.2%) at both locations.

Cherbal et al.[27]hows the impact of *P. lentiscus* L. hydro-methanolic leaf extract on the activities of α-amylase and sucrase enzymes. The extract reveals a good inhibition against α-amylase and sucrase activities, with a IC_{50} value of 5.81 mg/mL and 9.32 mg/mLrespectively. Therefore, higher inhibition is shown by the lower IC_{50} value, indi-

cating that the extract of *P. lentiscus L.* has more inhibitory effect on α-amylase than on sucrase.

An *in vitro* system with yeast cells suspended in a glucose solution in the presence or absence of the extract was used by the same authors [27]to examine the effect of *P. lentiscusL.* hydro-methanolic leaf extract on glucose transport across yeast cell membrane. The process by which glucose is transported across the yeast cell membrane is also being studied as an *in vitro* screening technique for the hypoglycemic impact of different compounds and medicinal plants. An indicator of the amount of glucose taken up by the yeast cells is the amount of glucose that is still in the medium after a specific time. The result showed that *P. lentiscus* L. extract possesses the ability to increase glucose absorbtion on yeast cells in a dose-dependent manner, strongly correlated with the concentration of the extract, reaching 92.85% at 50 mg/mL.

Furthermore, essential oils and volatile molecules as potential natural substance candidates, have recently attracted a lot of attention. In this context, El Omari et al.[34]examined the antidiabetic properties of the volatile components of *Pistacia lentiscus* essential oils (PLEOs), obtained from fruit extract and its main compounds, limonene and α-pinene. The results showed that PLEO along with and α-pinene (**1**) and limonene (**3**,**10**) exhibited promising antidiabetic potential, with IC_{50} values ranging from 78.03 ± 2.31 to 116.03 ± 7.42 μg/mL for α-glucosidase and from 74.39 ± 3.08 to 112.35 ± 4.92 μg/mL for α-amylase assay. In particular, limonene was found to be the most active compound, being the IC_{50} values equal to 78.03 ± 2.31 and 74.39 ± 3.08 μg/mL for α-glucosidase and α-amylase, respectively. This suggests that limonene could represent a promising target for the development of antidiabetic drugs.

Moreover, an effect of *P. lentiscus* toward α-glucosidase enzyme as target, has been reported in a cellular system [36]. In fact, this study reported the biological effects of Chios mastic extract in Caco-2 cells, a model of human small intestine mucosa. This extract, with very high contents of triterpenes, demonstrated to modulate glucose metabolism in Caco-2 cells by reducing disaccharidase activity along with sucrase–isomaltase expression.

Overall, these studies highlight that *Pistacia lentiscus* possess the ability to inhibit crucial gastrointestinal enzymes involved in carbohydrate digestion and absorption thus supporting its potential as antidiabetic agents which can be useful on the management of T2D.

3.1.2. Inhibition of lipase

Pancreatic lipase (PL, EC 3.1.1.3) represents another therapeutic target for the treatment of T2D. It is the key enzyme in lipid absorption, responsible for digestion of dietary triglycerides in the small intestine. PL catalyses the hydrolysis of triacylglycerols into free fatty acids and monoacylglycerols which can be absorbed by enterocytes[37]. Excessive lipids accumulation in the pancreas may contribute to insulin-producing β-cell dysfunction, characteristic of T2D. In this context, inhibitors of pancreatic lipase are attracting much research interest due to their anti-obesity activity by delaying the lipolytic process. This action would lead to the decrease in lipid absorption and thus protect the pancreas, which will restore regular insulin production from the β cells. On this basis, Foddai et al.[26] evaluated the inhibitory effect of *Pistacia lentiscus* leaves and fruits aqueous extracts against PL. The extracts exhibited highly significant *in vitro* dose-related inhibition of PL. Among them, *P. lentiscus* leaves reveled to possess a IC_{50} value of 6.1 ± 0.2 μg/mL, 20 times lower that *P. lentiscus* fruits (125.2 ± 12.1 μg/mL).

These results contribute to consider *Pistacia lentiscus* as potential candidate for the development of functional foods in obesity prevention and phytotherapy.

3.1.3. Inhibition of 11β-hydroxysteroid dehydrogenase 1

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1, E.C. 1.1.1.146) is an enzyme, mainly expressed in liver and adipose tissues, that catalyzes the conversion of inactive 11-ketoglucocorticoids into active 11β-hydroxy-forms. It is also known as cortisone reductase because it is a NADPH-dependent enzyme catalyzing the reduction of the inactive cortisone to the active cortisol. In contrast, 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) is an NAD^+-dependent dehydrogenase catalyzing the oxidation of cortisol to cortisone.

Since cortisol and glucocorticoids synthetized by 11β-HSD1 activity decrease glucose uptake and enhance liver gluconeogenesis, affecting carbohydrate and fat metabolism, increased enzymatic activity may result in obesity, insulin resistance and T2D[38]. Inhibition of 11β-HSD1 activity decreases insulin-resistance and glucose production representing a therapeutic target for the development of potential drugs for T2D. There are several known 11β-HSD1 inhibitors from synthetic or natural origin, the latter being mostly triterpenes. Mustic gum from *P. lentiscus* is rich in triterpenes and the 11β-HSD1 inhibitory activity were investigated[39]. Oleoresin, acidic fraction and two triterpenes isolated from the acidic fraction (masticadienonic and isomasticadienonic acids) showed to selectively inhibit 11β-HSD1 and not 11β-HSD2. The inhibitory activity was evaluated in lysed cells expressing 11β-HSD1. The IC_{50} values are reported and resulted to be 1.33 and 2.10 μg/mL for oleoresin and acidic fraction, and 2.51 and 1.94 μM for masticadienonic (**50**) and isomasticadienonic (**49**) acids, respectively. Moreover, docking analysis predicted the binding site of masticadienonic and isomasticadienonic acids and confirm that both compounds occupied the 11β-HSD1 binding site, therefore they inhibit the enzyme preventing the binding of its natural substrate [39].

Thus, one of the reasons why mastic gum is known for its anti-diabetic effect could be represented by 11β-HSD1 inhibition and the consequent regulation of glucocorticoid metabolism.

3.1.4. Biological activity towards PPARγ

The peroxisome proliferator-activated receptors (PPARs) are nuclear fatty acid transcription factors involved in several diseases. In particular, PPARγ is the most studied member of this family, which regulates glucose and lipid pathways with a high expression in adipose tissue and, to a lesser extent, in the liver and in the muscle. By binding to a specific ligand, PPARγ regulate the transcription of several target genes in tissues which are involved in lipid and glucose metabolism and homeostasis. PPARγ agonists, such as thiazolidinediones (TZD), act as insulin-sensitizing agents and are currently used in clinical practice for treatment of diabetes. They normalize the glucose profile promoting insulin-stimulated glucose uptake and suppressing hepatic gluconeogenesis[40]. Despite the beneficial effect of using such drugs, there are several undesirable side effects due to the use of TZDs, such as weight gain, fluid retention, heart failure, and hepatotoxicity. The activation of PPARγ is affected by the type of agonist which may be full or partial depending on the structural differences and activation profile. It has been reported that a partial agonist seems to induce less side effects as observed for the full agonist TZDs[41]. In this context, the identification of PPARγ partial agonists is a promising strategy for diabetes management.

Peterson and colleagues [41]conducted a virtual screening for novel PPARγ partial agonists and identified oleanonic acid (**46**) as a potential target molecule. Oleanonic acid is a triterpene found in the oleoresin of *Pistacia lentiscus* var. Chia. Neutral and acidic fraction of oleoresin showed to possess PPARγ activation properties. Specifically, a fraction of the acidic fraction almost exclusively contained oleanonic acid and was further characterized. Dose response analysis and competition assay using a standard full agonist suggested that this fraction containing oleanonic acid may function as a partial agonist for PPARγ. This result was confirmed by docking analysis of oleanonic acid which showed the aminoacidic interaction characteristic of a partial-agonist molecules.

Considering that this extract acts as partial PPARγ agonist, activity of this subfractions of *P. lentiscus* oleoresin was less than that of a full-agonist reference compound. Otherwise, it could contribute to the activities of the gum which has been described also towards other T2D therapeutic target (i.e., 11β-HSD1), confirming the beneficial antidiabetic properties of the Chios mastic gum.

3.2. In vivo experiments

3.2.1. Hypoglycaemic effect

To investigate the antiglycaemic effect of *P. Lentiscus* on mice, diabetes is induced using two primary techniques, alloxan and streptozotocin (STZ). The alloxan-induced diabetes technique involves a single intra-peritoneal injection of a freshly prepared alloxan solution at a dose of 150 mg/kg body weight. This compound, acting as a toxic glucose analogue, selectively accumulates in pancreatic beta cells via the GLUT2 glucose transporter. Upon entry into the beta cells, alloxan undergoes a cyclic redox reaction, facilitated by intracellular thiols such as glutathione, generating reactive oxygen species (ROS) and, ultimately, hydroxyl radicals. The ensuing oxidative stress leads to the death of beta cells, resulting in insulin-dependent alloxan diabetes. Notably, alloxan also inhibits glucose-induced insulin secretion by selectively targeting the beta cell glucose sensor glucokinase[42]. On the other hand, STZ-induced diabetes technique involves intra-peritoneal administration of STZ dissolved in a citrate buffer, typically at a dose of 60 mg/kg. Following uptake into beta cells, STZ undergoes enzymatic cleavage, separating into its glucose and methylnitrosourea components. The latter, with potent alkylating properties, induces damage to biological macromolecules, including DNA fragmentation, leading to beta cell destruction and the onset of insulin-dependent diabetes[43].

In the murine model of alloxan-induced diabetes, various experiments have explored the use of *P. lentiscus*. One study treated mice with a hydro-methanolic leaves extract at 300 mg/kg, resulting in a significant 36% reduction in blood glucose levels and an accompanying increase in plasma insulin levels[27]. Another study on crude Pistacia gum treatment at 100 mg/kg in diabetic mice showed significantly lower blood glucose levels compared to untreated diabetic mice with crude *P. lentiscu*s showing comparable effectiveness to the anti-diabetic drug glibenclamide in maintaining glucose homeostasis[44]. This study also assessed liver function markers alanine transaminase (ALT) and aspartate transaminase (AST) levels, which were significantly lowered in *P. lentiscus*-treated group at 21st day as compared to diabetic untreated and glibenclamide-treated groups.

In the murine model of STZ-induced diabetes, treatment with ethanol extracts of *P. lentiscus* leaves and fruits at concentrations of 50 mg/kg and 125 mg/kg, demonstrated a substantial reduction in blood glucose levels comparable to the reference drug glibenclamide. Additionally, flower extracts exhibited a milder effect, while leaves extracts restored blood glucose to normal values after a two-hour treatment, emphasizing their efficacy in diabetes management[28].

Several clinical studies have demonstrated the anti-hyperglycemic effects of Chios Mastic gum on human volunteers[35].

In a prospective, randomized, placebo-controlled pilot study involving 156 volunteers with total cholesterol levels >200 mg/dl were divided into four groups: control group (receiving placebo), total mastic group (receiving 1 g of total crude mastic gum capsules three times daily), polymer-free mastic group (receiving 1 g of polymer-free mastic capsules three times daily), and powder mastic group (receiving 2 g of crude mastic gum daily). After eight weeks, the total crude mastic gum group showed a significant reduction in fasting plasma glucose by 4.5 mg/dl ($p < 0.05$), particularly in overweight and obese individuals with body mass index, BMI > 25. The other groups did not exhibit significant alterations in glucose levels, although there was a trend towards re-

duction. No adverse events were reported, and there were no changes in BMI, liver enzymes, or renal function markers[35].

In another double-blind, placebo-controlled, randomized trial involving healthy Japanese men over 40 years old, Chios mastic gum intake alone and in combination with physical activity led to significant reductions in insulin levels, and insulin resistance compared to a control group. Specifically, CMG intake alone reduced insulin resistance values at 6 months. Moreover, CMG intake combined with exercise reduced insulin resistance already at 3 months, suggesting its importance, along with physical activity, in effectively managing glucose metabolism[45].

3.2.2. Hypolipidemic effect

Several studies have investigated the hypolipidemic effects of *Pistacia lentiscus*, both in animal models and human subjects, highlighting its potential therapeutic value in managing lipid-related disorders.

In mice with induced hypercholesterolemia by administering food containing high cholesterol (1%) for thirty days, administration of aqueous leaves extract of *P. lentiscus* resulted in significant reductions in total cholesterol (from 253 ± 31.60 mg/dL to 154.6 ± 18.10 mg/dL), triglycerides (from 200 ± 12.32 mg/dL to 97.6 ± 3.57 mg/dL), and LDL-cholesterol levels (from 160 ± 31.60 to 145.88 ± 9.76 mg/dL). Similarly, treatment with ethanolic leaves extract significantly decreased total cholesterol (154.6 ± 18.10 mg/dL), triglyceride (71.2 ± 4.38 mg/dL), and LDL-cholesterol (99.36 ± 18.77 mg/dL) levels compared to the hypercholesterolemic control group, indicating its potential as a hypolipidemic agent[46]. In STZ-induced diabetic mice low and high doses of Chios mastic gum resulted in improvements in lipid profiles. After 4 weeks of CMG administration, serum triglyceride levels were significantly reduced in both the low-dose and high-dose treated groups compared to the control group. Additionally, at the end of the 8-week study period, the low-dose treated group exhibited further improvements in serum total cholesterol, LDL, and triglyceride levels, along with increased HDL levels compared to the control group[47].

In rabbit models, mastic total extract without polymer and its neutral fraction demonstrated significant reductions in myocardial infarction size and atherosclerosis, alongside notable hypolipidemic effects in hypercholesterolemic rabbits. Additionally, histological analysis revealed a reduction in subintimal lipid accumulation and foamy macrophages in aortic tissue samples from rabbits treated with both extracts, suggesting anti-atherosclerotic and anti-lipidemic properties[48].

Likewise, in rabbits fed with a hyperlipidemic diet containing egg yolk, *P. lentiscus* fatty oil was administered. The results showed that egg yolk consumption significantly elevated total cholesterol, triglycerides and LDL/HDL ratio compared to the control group. However, treatment with *P. lentiscus* fatty oil or simvastatin significantly reduced total cholesterol, triglycerides and LDL. Specifically, triglycerides levels decreased by 50.75% compared to egg yolk consumption group without fatty oil. No significant changes were observed in HDL levels[32].

CMG has been extensively studied in several randomized controlled trials to assess its effects on lipid and glucose metabolism, as well as its potential therapeutic benefits in managing various metabolic disorders. In the study described in the previous section (Section 3.2.1.) involving healthy Japanese men over 40 years old, CMG intake alone and in combination with physical activity as well as manage glucose metabolism, also led to significant reductions in serum triglycerides[45].

Another *in vivo* human study focused on Chios Mastiha Essential Oil (CMEO) demonstrated significant improvements in blood lipid profile, including reductions in triglycerides and LDL, along with other metabolic markers in individuals with abdominal obesity and metabolic abnormalities. Moreover, it was found a decrease in systolic blood pressure and ALT levels only after CMEO intake, reduction in weight, % body

fat, and visceral fat and also improvement in health-related quality of life scores, both physical and mental, in the CMEO group compared to controls[49].

Furthermore, total mastic gum also showed the ability to reduce total cholesterol levels by 11.5 mg/dl ($p < 0.05$), with a stronger effect observed in overweight and obese individuals[35].

Finally, 133 participants aged over 50 were randomly assigned to either a high-dose group consuming 5 g of mastic powder daily or a low-dose group receiving a Chios mastic solution. Throughout the study duration, the high-dose group exhibited significant reductions in total cholesterol, LDL, total cholesterol/HDL ratio, lipoprotein, apolipoprotein A-1, apolipoprotein B, SGOT, SGPT, and gamma-GT levels. However, glucose, HDL, and triglyceride levels remained unchanged in this group. Interestingly, only male subjects in the low-dose group displayed a notable decrease in serum glucose levels. These findings suggest potential benefits of Chios mastic powder in improving lipid profiles and hepatic enzymes[50]. Further research is necessary to fully elucidate these effects and their clinical implications.

All the antidiabetic activities of *Pistacia lentiscus* extracts or isolated compounds are reported in Table 2 together with identified compounds for each active extract, where reported in the literature.

Table 2. Biological activities of extracts or single compounds of *Pistacia lentiscus* and chemical composition identified in different parts of the plant.

Anti-diabetic activity						
Plant Part	**Origin**	**Type of extract/ Active compounds**	**Compound**	**Results**		**References**
Leaves	Algeria	Methanolic	Gallic acid (107) Vanillic acid (108) *p*-Coumaric acid (113) Caffeic acid (114)	Inhibition of α-amylase and sucrase. Increase of glucose transport across the yeast cell membrane	*In vitro*	[27]
				Hypoglycaemic effect: reduction in blood glucose level and increase in insulin level	*In vivo* (Rat)	
Leaves	Algeria	Aqueous and ethanolic	n.r.	Hypolipidemic effect: reduction in triglycerides, total cholesterol and LDL-cholesterol levels	*In vivo* (Mice)	[46]
Leaves	Italy (Sardinia)	Aqueous	Myricetin (127) Quercetin-3-*O*-rutinoside (rutin) (128) Quercetin 3-*O*-glucoside (129) Myricetin 3-*O*-rhamnoside (135) Myricetin 3-*O*-rutinoside (138) Quercetin-3,4′-diglucoside (140) Quercetin-3-*O*-galactoside (141) Myricetin-3-*O*-arabinopyranoside (142) Myricetin-3-*O*-xylopyranoside (143)	Inhibition of α-amylase and α-glucosidase. Inhibition ofpancreaticlipase	*In vitro*	[26]

Fruits			Gallicacid (107) Quercetin-3-*O*-rutinoside (rutin) (128) Quercetin 3-*O*-glucoside (129) Myricetin 3-*O*-glucoside (134) Luteolin-3′-*O*-glucoside (139) 3,5-Digalloyl quinic acid (163) 3-Galloyl quinic acid (165) 5-Galloyl quinic acid (166) 1,5-Digalloyl quinic acid (170)			
Fruits	Morocco	Essentialoils	α-Pinene(1) (R) Limonene (3) (S) Limonene (10)	Inhibition of α-amylase and α-glucosidase	*In vitro*	[34]
Leaves Fruits	Algeria	Ethanolic	Salicylic acid (106) Gallic acid (107) Syringic acid (110) 3,4-Dihydroxyhydro-cinnamic acid (116) Ellagic acid (117) Luteolin (122) Catechin (124) Quercetin 3-*O*-rhamnoside (136)	Inhibition of α-amylase	*In vitro*	[28]
				Hypoglycemic effect: reduction in blood glucose level	*In vivo* (Mice)	
Leaves Stem barks Fruits	Algeria	Methanolic	3,5-Digalloyl quinic acid (163) Epigallocatechin(4a>8)epigallocatechin (144) (Epi)gallocatechin-3-*O*-galloyl-(Epi)gallocatechin (145)	Inhibition ofα-glucosidase	*In vitro*	[1]
Black fruits	Algeria	Deep EutecticSolvent (DES)	Catechol (100) Gallic acid (107) Cinnamic acid (112) Coumaric acid (113)	Inhibition of α-amylase	*In vitro*	[25]

			Caffeic acid (114) Kaempferol (123) Catechin (124) Quercetin (125) Rutin (128) Cyanidin-3-*O*-glucoside (131) Chrysin (146) Silymarin (147) Deosmin (148) Ascorbic acid (176) Citric acid (177) Pyrogallic acid (178) Tartaric acid (179 Curcumin (180) 3,5-Dimethoxy-4-hydroxy-tannic acid (168) Tannic acid (169)			
Black fruits	Algeria	Fatty oil and unsaponifiable matter	n.r.	Inhibition of α-amylase and α-glucosidase	*In vitro*	[33]
Chios masticgum	n.r.	Oleoresin and its neutral and acidic fraction/Oleanoic acid	Oleanoic acid (51)	PPARγagonists	*In vitro* Virtual screening	[41]
Chios mastic gum	n.r.	Oleoresin and its acidic fraction/ Masticadienonic and isomasticadienonic acid	28-Norolean-17-en-3-one (45) Isomasticadienonic acid (49) Masticadienonic acid (50) Oleanolic acid (51) Masticadienolic acid (92) 3-Epimasticadienolic acid (96)	Inhibition of 11β-HSD1	*In vitro* Virtual screening	[39]

			Methyl 3-epimasticadienolate (97)			
Chios mastic gum	Italia	Supermastic	Oleanonic acid (46) Moronic acid (47) Maslinic acid (48) Isomasticadienonic acid (49) Masticadienonic acid (50) Oleanolic acid (51) Masticadienolic acid (92) Isomasticadienolic acid (93)	Inhibition of disaccharidase activity in Caco-2 cells Reduction in sucrase-isomaltase expression	*In vitro*	[36]
Chios mastic gum	Pakistan	Crude gumpowder	n.r.	Hypoglycaemic effect: reduction in blood glucose level	*In vivo* (Rat)	[44]
Chios mastic gum	Greece	Crude gum	n.r.	Hypoglycemic and hypolipidemic effect: reduction in blood glucose level and reduction of serum triglyceride, total cholesterol and LDL levels.	*In vivo* (Mice)	[47]

Chios mastic gum	Greece	Total mastic extract without polymer	28-Norolean-17-en-3-one (45) Oleanoic acid (46) Moronic acid (47) 24Z-Isomasticadienoic acid (49) 24Z-Masticadienoic acid (50) Olean-12,18-dien-3-olic acid (94)	Hypolipidemic effect: reduction in total cholesterol and LDL circulatory levels	*In vivo* (Rabbit)	[48]
		Neutral mastic fraction	Butyrospermol (55) Oleanolic aldehyde (57) β-Amyrone (59) Betulonal (61) Tirucallol (63) Dammaradienone (64)			
Fruits	Algeria	Fatty oil	Oleic acid (150) Palmitic acid (154) Linoleic acid (152)	Anti-hyperlipidemic effect: reduction total cholesterol, LDL-cholesterol and triglycerides level	*In vivo* (Rabbit)	[32]
Chios mastic gum	Greece	Crude gumpowder	n.r.	Hypoglycemic and hypolipidemic effect: reduction in blood glucose and total colesterol level.	*In vivo* (Human)	[35]
Chios masticgum	Japan	Capsules of gumpowder	Camphene (7) Verbenone (15) Linalool (39) α-Terpinolene (42) 28-Norolean-17-en-3-one (45) Moronic acid (47) Masticadienonic acid (50) Oleanolic acid (51) Oleanolic aldehyde (57) β-Amyrone (59)	Hypoglycaemic and hypolipidemic effect: reduction in insulineresistence and reduction of serum triglicerides	*In vivo* (Human)	[45]

			Tirucallol (63) Dammaradienone (64) Masticadienolic acid (92) Isomasticadienolic acid (93) Isomasticadienolic aldehyde (95)			
Chios mastic gum	n.r.	Masticsolution	n.r.	Hypoglycemic and hypolipidemic effect: reduction in blood glucose level and total cholesterol, LDL, total cholesterol/HDL ratio	*In vivo* (Human)	[50]
Chios mastic gum	n.r.	Essential oils in gel capsules	α-*Pinene* (1) β-Pinene (2) (R) Limonene (3) β-Mircene (4) Camphene (7) (-) β-Caryophyllene (28) (+) β-Caryophyllene (29) α-*Thujene* (43) *o*-Methylanisol (175)	Hypolipidemic and anti-obesity effect: reduction of triglycerides and LDL	*In vivo* (Human)	[49]

n.r.: data not reported in literature.

4. Conclusions and Future Directions

The present review highlighted the promising health-promoting activities of *P. lentiscus* in T2D treatment. *P. lentiscus* has been recognized as an herbal medicine for different disorders and here we presented all the available information concerning its antidiabetic properties. In fact, several extracts and compounds from different parts of the plant showed activity against one or more targets implicated in T2D treatment. Unlike T1D, T2D is a complex pathology which need a combination therapy by using two or more drugs against totally different targets in order to reduce hyperglycemia and hyperlipidemia, both contributing to diabetic disease. While combination therapy can be effective, it often exacerbates side effects. The ultimate objective in T2D management is to identify a single drug capable of acting on multiple targets to mitigate the complications associated with polypharmacy. As reported from the literature, *P. lentiscus* showed *in vitro* (in cell-free and in cellular systems) and *in vivo* activities towards more targets, emerging as a good candidate for multitarget drug discovery in T2D treatment.

Additionally, we have compiled a summary of the compounds found in *P. lentiscus* and the extracts in which each compound has been identified. Thus, from the analysis of all the data present in the literature, one future perspective could be to identify which compounds are responsible for the activities of the extracts with the possibility of identifying novel and potent active molecules.

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