Pharmacological and Biological Activities

A polymeric procyanidine glycoside, isolated from *Pistacia lentiscus* was shown to have hypotensive activity (Sanz *et al*., 1992,1993). It also inhibited the hypertensive response to angiotensin I, indicating the possible involvement of angiotensin system in its mechanism of action (Sanchez *et al*., 1993).

The resin of *Pistacia lentiscus* has antioxidant and antimicrobial activities (Magiatis *et al*., 1999; Kordali *et al*., 2003). The essential oil of the plant did not show any activity against Gram-negative and Gram-positive bacteria, while the phenolic fraction displayed significant inhibitory activity against *Bacillus stearothermophilus, Hafnia alvei, Klebsiella oxytola* and *Sarcina lutea* (Bonsignore *et al*., 1998b). The antimicrobial activity of the essential oil of mastic gum, was greater on Gram negative bacteria (Tassou and Nychas, 1995). The minimum inhibitory concentration values of the leaf essential oil against four Gram negative bacteria *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia* and *Salmonella typhi* and five Gram-positive: *Staphylococcus aureus, Staphylococcus intermedius, Enterococcus faecalis, Bacillus sphericus* and *Enterobacter aerogenes*, ranged from 0.08 to 1.56 mg/mL (Derwich *et al*., 2010). The study of Takhi *et al*. (2011) showed that the essential oils of *Pistacia atlantica* and *Pistacia lentiscus* had an inhibiting activity against *Escherichia coli, Staphylococcus aureus Pseudomonas aeruginosa* and *Fusarium oxysporum* f. sp. *albedinis* and *Fusarium oxysporum* f. sp. *lycopersici*. The minimum inhibitory concentration of *Pistacia lentiscus* essential oil on bacteria was 0.25% (vol./vol.) (Takhi *et al*., 2011). The oil showed strong activity against *Klebsiella pneumonia* (Mharti *et al*., 2011).

Pistacia lentiscus oil has been found as partially help in the protection against mercury intoxication as in the case of alkaline phosphatase, aspartate aminotransferase and urea, and it could also be considered a safe nutritional source, at least by maintaining total cholesterol and LDL-cholesterol in their normal ranges (Tounes *et al*., 2008). The fruit's fatty oil, and in particular the unsaponifiable fraction, showed dermal wound healing activity (Boulebda *et al*., 2009).

The acid fraction of the total Chios mastic gum (resin of *Pistachia lentiscus* var. *chia*), without polymer (TMEWP) was found to be the most active extract (minimum bactericidal concentrations "MBC", 0.139 mg/mL), and the most active pure compound was isomasticadienolic acid (MBC, 0.202 mg/mL [0.443 mM]). The results obtained by Paraschos *et al*. (2007) showed that administration of TMEWP may be effective in reducing *Heliobacter pylori* colonization and that the major triterpenic acids in the acid extract may be responsible for such an activity. The antibacterial activity of the arabino-galactan proteins, isolated from *Pistacia lentiscus* var. *chia*, against *Helicobacter pylori* was also reported (Kottakis *et al*., 2008). The antifungal activities of oil of the plant as well as the resin (total, acidic and neutral fractions) against the growth of three agricultural pathogens (*Fusarium sambucinum, Phythium ultimum* and *Rhizoctonia solani*) have been investigated. The leaf oil as well as some of the resin fractions significantly inhibited the growth of *Rhizoctonia solani*. However, all samples did not show antifungal activity against *Fusarium sambucinum* and *Phythium ultimum*, but increased the growth of *Fusarium sambucinum* (Duru *et al*., 2003). Also, Kordali *et al*. (2003) found that different leaf extracts of the plant inhibited the growth of *Rhizoctonia solani* between the range of 24 and 48%.

Aqueous and flavonoid-enriched extracts as well as essential oil (EO) obtained from leaves of *Pistacia lentiscus* possessed antibacterial and antimutagenic activities (Ben Douissa *et al*., 2005; Hayder *et al*., 2005). A marked inhibitory effect was observed against

Salmonella typhimurium, whereas lower activity was observed against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella enteritidis*. The EO showed significant inhibitory effects against *Salmonella typhimurium*, *Salmonella enteritidis* and *Staphylococcus aureus*. The antimutagenic activity of the different extracts againsta aflatoxin B1 (AFB1) and sodium azide was demonstrated with the *Salmonella typhimurium* assay (Hayder *et al*., 2005). The study of the *in vitro* antimicrobial activity of *Pistacia lentiscus* L. extracts, revealed that the decoctions showed the best antibacterial activity against bacteria (*Sarcina lutea*, *Staphylococcus aureus* and *Escherichia coli*) and fungi (*Candida albicans*, *Candida parapsilosis*, *Torulopsis glabrata* and *Cryptococcus neoformans*), However, the activity against fungal cells appears to be much more interesting (Iauk *et al*., 1996). The antimicrobial activity of the essential oil from both leaves and the mastic gum, as well as of the other constituents of *Pistacia lentiscus* has been reported by others (Ali-Shtayeh and Abu Ghedib, 1999; Marone *et al*., 2001; Rossi *et al*., 2007; Basal *et al*., 2010).

Pistacia lentiscus has been reported as a considerable source of natural antioxidants (Benhammou *et al*., 2007). The antioxidant activity of the essential oil, phenolic constituents and extracts of *Pistacia lentiscus* has been proved by several researchers (Bratto *et al*., 2003; Assimpoulou *et al*., 2005; Ljubuncic *et al*., 2005; Abdelwahed *et al*., 2007; Longo *et al*., 2008; Atmani *et al*., 2009; Bhouri *et al*., 2010; Mahmoudi *et al*., 2010; Djenane *et al*., 2011, 2012; Piluzza and Bullitta, 2011; Sharifi and Hazell, 2012). Digallic acid, isolated from the fruits induces apoptosis and enhances antioxidant activities (Bhouri *et al*., 2012a), and has the potential as a cancer- protective agent (Bhouri *et al*., 2012b).

Belloni Regazzo (2005) reported natural products or pharmaceutical compositions containing plant essential oil, from *Pistacia terebinthus*, *Pistacia lentiscus*, *Pistacia vera*, *Pistacia integerrima* or other *Pistacia* species, or their components, natural or synthetic, or mixture or derivatives thereof, for the prevention and treatment of cancer. The results obtained by Loutrari *et al*. (2006) also underscore that mastic oil from *Pistacia lentiscus* var. *chia*, through its multiple effects on malignant cells and ECs, may be a useful natural dietary supplement for cancer prevention. An anticancer compound, isolated from Chios mastic gum, is effective against various types of cancer cells, including human colon cancer cells (Pantazis *et al*., 2005). The findings of Balan *et al*. (2007) demonstrated that a 50% ethanol extract of the plant-derived product, Chios mastic gum (CMG), contains compounds which inhibit proliferation and induce death of HCT116 human colon cancer cells in vitro. CMG-treatment induces cell arrest at G1, detachment of the cells from the substrate, activation of pro-caspases-8, -9 and -3, and causes several morphological changes typical of apoptosis in cell organelles. The findings presented here suggest that CMG (a) induces an anoikis form of cell death in HCT116 colon cancer cells that includes events associated with caspase-dependent pathways; and (b) might be developed into a chemotherapeutic agent for the treatment of human colon and other cancers. The cytotoxicity of *Pistacia lentiscus* has been reported by others (Ljubuncic *et al*., 2005; Longo *et al*., 2008; Sakagami *et al*., 2009).

The resin of *Pistacia lentiscus* var. *chia* has been used for more than 2500 years in traditional Greek medicine for treating several diseases such as gastralgia and peptic ulcers, while the actions of the gum are mentioned in the works of Herodotus, Dioscorides and Galen. Several Roman, Byzantine, Arab and European authors make extensive refs. to mastic's healing properties. Modern scientific research has justified the beneficial action of mastic to gastric diseases, by revealing its in vivo and in vitro activity against Helicobacter pylori, which is considered as the main cause for gastric ulcers. Furthermore, studies of the antimicrobial, antifungal, antioxidant, hypolipidemic, anti-inflammatory, anti-Crohn and anticancer activities of mastic have characterized it as a wide-range therapeutic agent and a potential source of nature-originated treatments (Paraschos *et al*., 2012). The most

comprehensive data so far have indicated that mastic gum provides protection against gastrointestinal malfunctions and bacterial infections. Substantial evidence has also suggested that mastic gum exhibits hepatoprotective and cardioprotective, antiinflammatory/antioxidant, and antiatherogenic properties. In the last decade, an increasing no. of studies further evaluated the potential antiproliferative properties of mastic gum against several types of human neoplasia. The present review aims to summarize the current data concerning the anticancer activities of mastic gum and their major constituents, highlighting also the mol. mechanisms through which they exert anticancer function. Mastic gum constituents that belong to the chem. class of triterpenoids appear to be mainly responsible for its anticancer potential. Chios mastic gum could be considered as a conglomeration of effective anticancer drugs (Giaginis and Theocharis, 2011). Compositions containing acid extracts of mastic gum are used for treatment of neurological diseases (Hazan and Lucassen, 2012).

The mastic gum of *Pistacia lentiscus* produced significant anti-inflammatory activity (Mahmoudi *et al*., 2010; Qiao *et al*., 2011). Both the essential oil of *Pastacia lentiscus* (Maxia, 2011) and the gum of Chios mastic (*Pastacia lentiscus* var. *chia*) (Castanas, 2008a,b; Triantafyllou *et al*., 2011) are used for the treatment and prevention of inflammation. Moon *et al*. (2010) described a pharmaceutical preparation, for mastic (*Pistacia lentiscus*) for treating ulcerative colitis and Crohn disease. *Pistacia lentiscus* possesses the following activities: anthelmintic (Landau *et al*., 2010; Manolaraki *et al*., 2010), antitherogenic (Dedoussis *et al*., 2004), antiulcer (Al-Said *et al*., 1986), antimutagenic (Marone *et al*., 2001; Hayder *et al*., 2005; Abdelwahed *et al*., 2007), hepatoprotective (Janakat and Al-Merie, 2002), antigenotoxic (Bhouri *et al*., 2010) and insecticidal (Yildirin *et al*., 2005; Bachrouch *et al*., 2010). *Pistacia lentiscus* virgin fatty oil promotes significantly ($p < 0.05$) wound contraction and reduces epithelization period in rabbit model (Djerrou *et al*., 2010). Acute and oral toxicity, irritation, sensitization, phototoxicity, pharmacological and regulatory status information on mastic gum of *Pistacia lentiscus* have been reviewed and was found acceptable for use in foods in Europe (Ford, 1992).

The oil obtained from the fruit can be used alone or by combination, and has the effects of softening skin and increasing skin luster. It is especially suitable for sensitive skin. It can be prepared into soap, shampoo or emollient water (Faure, 1982). The resin has been used in cancer, infection, surgical wound adhesion, and ulcers. Studies also document its use an antioxidant and an insecticide, and for treatment of high cholesterol, Crohn disease, diabetes and hypertension (Drugs.com, mastic, 2012).

The effect of *Pistacia lentiscus* leaf extracts (aqueous, 30% ethanol and 70% ethanol) was studied on the rat isolated trachea. The extracts induced a relaxation on basal tone and precontracted trachea. On the rat isolated trachea precontracted by acetylcholine 10-3 M, leaf extracts (aqueous, 30% ethanol and 70% ethanol) induced a relaxation. On precontracted rat trachea, adenosine induced contractile response and predominant relaxation. *Pistacia lentiscus* blocked adenosine contractile response and potentiated the purine nucleoside relaxation (Fehri and Aiache, 2008). Acute treatment of the essential before bilateral common carotid artery occlusion/reperfusion (BCCAO/R) elicits changes both in the frontal cortex, where the BCCAO/R induced decrease of docosahexaenoic acid (DHA) is apparently prevented and cyclooxygenase-2 (COX-2) expression decreases, and in plasma, where palmotylethanolamide (PEA) and oleoylethanolamide (OEA) levels and DHA biosynthesis increase. It is suggested that the increase of PEA and OEA plasma levels may induce DHA biosynthesis via peroxisome proliferator-activated receptor (PPAR) alpha activation, protecting brain tissue from ischemia/reperfusion injury (Quartu *et al*., 2012).

Consumption of *Pistacia lentiscus* foliage alleviates coccidiosis in young goats

(Markovics *et al*., 2012). Also, two cases of acute generalized exanthematous pustulosis induced by ingestion of the essential oil were reported (Zaraa *et al*., 2012).

The herbal formulation (consisting of *Pistacia lentiscus* and 4 other herbs) exerted a highly significant hypoglycemic effect in experimental animals (Eskander *et al*., 1995). The therapeutic uses of mastic gum fractions from *Pistacia lentiscus* containing polymeric myrecene, was reported (Hazan, 2010).