Chios Gum Mastic: A Review of its Biological Activities

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Abstract: The resin of *Pistacia lentiscus* (L.) var. *chia* (Duham), an evergreen shrub belonging to the family Anacardiaceae and uniquely cultivated in southern Chios, is known as mastic. It 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 references 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.

Keywords: Anti-cancer activity, anti-helicobacter pylori activity, anti-inflammatory activity, mastic, mastic acidic fraction, mastic neutral fraction, Pistacia lentiscus (L.) var. chia.

INTRODUCTION

Pistacia lentiscus is an evergreen shrub of the Anacardiaceae family, which is common in the eastern Mediterranean area. The variety chia (Duham), commonly known as mastic tree, is uniquely cultivated in southern Chios, a Greek island in the Aegean. Mastic is the natural gum obtained as an exudate after "hurting" the trunk and branches of *P. lentiscus* (L.) var. chia (Figs. **1**,**2**).

It is more than 2500 years that gum mastic has been used in traditional Greek medicine, mainly for gastrointestinal disorders like peptic ulcer and gastralgia. The works of Greek physicians, such as Dioscorides and Galen include mastic as an important healing factor, mention its properties and recommend its use. Today, it is used as a seasoning in Mediterranean cuisine, in the production of natural chewing gum, in perfumery, in dentistry, and also for the relief of gastralgia and protection against peptic ulcer in Greek traditional therapy.

The uninterrupted use of mastic, both in Europe and the Middle East area, reaches our era and covers a wide field of medical applications, thanks to the several healing properties of the gum. These properties have been the object of numerous researches, affording a great amount of scientific literature (see Table **1**).

Since the most common therapeutic use of mastic has historically been the one for gastrointestinal disorders, the first detailed studies of its activities would be targeting on this field specifically. Researches as those of Al-Habbal *et al* in 1984 [1] and Al Said *et al* in 1986 [2], coming from countries with a long tradition in the use of mastic, gave the initiative for further investigation and resulted to the correlation of mastic's effect on ulcer with its anti-*H.pylori* activity, with the article of Huwez *et al* in 1998 [3] constituting a turning point in the mastic research field.

In parallel with the anti-*H.pylori* activity, the effect of mastic and its essential oil, mastic oil, on other pathogenic bacteria, both Gram-negative and Gram-positive has made up for a number of interesting studies [4, 5].

The traditional use of mastic as a food preservative led to the discovery of its antioxidant activity by Abdel-Rahman *et al* [6] and triggered a series of studies concerning its hypolipidemic [7, 8] and anti-inflammatory activity [9, 10], which are complementary attributing mastic a potential cardioprotective role.

Fig. (1). The resinous exudate obtained after "hurting" the trunk and branches of *Pistacia lentiscus* (L.) var. chia, the coagulation of which affords gum mastic.

Other diseases, as Crohn's disease, also seem to constitute potential future targets of mastic's therapeutic capacity, as it has been shown by Kaliora *et al* [11, 12], while the anti-cancer activities of mastic, especially against colorectal [13, 14] and prostate cancer [15, 16, 17] have been already justified.

As our laboratory is specialized in the research of natural products and their biological activities [18, 19, 20, 21, 22], we evaluated mastic as an important source of extracts and pure compounds bearing biological and potentially pharmacological properties, and included it in our field of scientific interests as early as the late 1990's. This occupation yielded several publications that concerned the chemical composition and biological activities of both mastic oil [5] and gum mastic [23, 10]. Recently, mastic water, the condensed water vapour phase obtained together with mastic oil during the steam distillation of mastic resin, was also studied in our laboratory and a publication concerning its chemical composition and antimicrobial properties was issued [24]. As a continuation of our contribution in the research of the therapeutic effects of such an

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Fig. (2). Gum mastic tears, together with mastic tree leaves.

Table 1. Biological Activities of Mastic and its Fractions and Compounds

Biological Activity	Mastic/Fraction/Compound	Reference No
Anti-ulcer	mastic	[1], [2]
Suppression of induced intestinal damage	mastic	[33]
Anti-indigestion	mastic	[34]
Anti-*H.pylori*	mastic	[3], [37], [38]
	AGP's*	[39], [40]
	TMEWP**	[23]
	mastic acidic fraction	[23]
	isomasticadienolic acid	[23]
	polymer	[43]
	mastic	[44]
Antimicrobial	mastic	[45]
	mastic oil	[4], [5], [47]
Antifungal	mastic aqueous extract	[46]
Antioxidant	mastic	[6], [48], [49], [50]
Hypolipidemic	mastic total polar extract	[7]
	mastic	[8]
Anti-inflammatory	mastic	[9]
	mastic neutral fraction	[10]
	tirucallol	[10]
Anti-Crohn's disease	mastic	[11], [12]
Anti-prostate cancer	mastic	[15], [16], [17]
Anti-colorectal cancer	mastic hexane extract	[13], [14]
	mastic 50% ethanol extract	[51]
Anti-leukemic	mastic oil	[52]
Anti-lung carcinoma	mastic oil	[53]
Allergenic	mastic	[54], [55]
Hepatotoxic	mastic	[56], [57]

*arabinogalactan-proteins.

**Total Mastic Extract Without Polymer [23].

important natural product, characteristic of Greek agricultural production, we herein summarize the most important studies published about mastic's biological properties, together with a brief review of the healing uses of mastic throughout history and its role in Greek and Eastern Mediterranean therapeutic tradition.

HISTORICAL USES OF MASTIC

Mastic in Antiquity – Greeks, Romans, Egyptians

The oldest historical reference about the use of mastic seems to be that of Herodotus (5th c. B.C.), who informs us about chewing (mastication) of the dried resinous fluid secreted by the bark of the mastic tree. It is also possible that the *gum* used by ancient Egyptians to spread over the sheets covering embalmed corpses and that Herodotus mentions is actually mastic. Modern archeological findings aided by gas chromatography [25] have confirmed the use of mastic for embalmment of Egyptians mummies of the 7th c. B.C., by determining it as the main component of the mixture used.

Dioscorides (1st c. A.D.), one of the most exceptional medical authors of classical antiquity, made extended references to mastic, by attributing to *schinin*, as he named it, numerous therapeutic properties: beneficial for blood coagulation, for healing chronic cough, for stomach aches; also useful for cleaning the teeth, odoring the mouth when chewed and giving glow to the face when used as an ointment.

In his famous work "De Materia Medica", Dioscorides mentioned "*mastichinon elaion (oleum)*", probably a preparation received by mixing mastic with olive oil, and its warming, astringent and emollient properties, as well as its effect on inflammations of the stomach and on abdominal and intestinal disorders. He strongly emphasized that the best "mastichinon elaion" was produced in Chios. Dioscorides also reported adulteration of gum mastic with pine resin or frankincense, making one of the first references of natural product adulteration, a matter that has been worrying both the commercial and academic fields for centuries.

One century later, Galen mentioned "white mastic", which was produced in Chios, and attributed to it properties as emollient and styptic, which make it suitable for inflammations of the stomach, the abdomen and the liver. Galen also gave a prescription for healing stomach aches that contained mastic, as well as mandragora root and chrysobalanon, and recommended it as an antidote for snake bites.

In addition to ancient Greek physicians, their Roman colleagues as Plinius emphasized the use of mastic and its superiority to other resins. Plinius is probably the first author who reported the unique cultivation of mastic tree in the southern part of Chios. His reference about the use of mastic as an additive of grape must was confirmed by archeological findings of the 6th c. B.C. in dell' Osteris area in Italy [26], where FT-IR analysis of the residue in wine vessels revealed the presence of mastic.

The FT-IR and GC-MS analysis of an ointment found in an *unguentarium* in an Etrurian tomb of the 2nd c. B.C. in Chiusi, Italy [27], revealed mastic as one of the compounds. This is probably the oldest cosmetic preparation containing mastic discovered until now.

Middle Ages – Byzantine and Genovese Period

During the byzantine era, the trade and use of mastic was extended and very profitable for the imperial treasury, acquiring 120.000 golden tokens annually [28] (Savvidis 2000). Its uses in stomach aches, mouth hygiene, facial creams, production of soap, tooth paste and even as a *panacea* (especially for pathological cases with no confirmed cause) were mentioned by contemporary authors [29].

After the occupation of the island of Chios by the Genovese, exploitation of mastic passed first to the house of the Zaccaria and later to the one of the Giustiniani. The prosperity of the production allowed the expansion of mastic's trade to the Islamic world, where mastic was already popular for chewing and odoring the mouth and also as an additive in bread, due to a recommendation for its use by Mohammed himself in the Quran. During the Giustiniani period, mastic was exported all over Europe, but the price paid by the population of Chios for this "flourishing" was exhausting (slavish working conditions, excessive taxing, severe punishment for stealing). This "colonialist" behavior made the locals see the change of power to the Ottoman Turks even as comforting.

Ottoman Period

The use of most of the production of mastic for the Sultan's harem was the main reason for awarding privileges to the island and its inhabitants, starting from 1567, with low taxing rate being the most important. Unfortunately, this period was also characterized by autarchic violence, with the Destruction of Chios by the Ottomans in 1822 being the most serious case. This incident caused the devastation of the island and the total annihilation of mastic production, which took decades to recover.

Numerous European authors of the Ottoman period mentioned several applications of mastic, as the addition in wine and alcoholic preparations by André Thévet in 1549, the use in healing ointments by Louis Chevalier in 1669, the addition in bread by Francesco Piacenza in 1688 and Jullien Galland in 1747 [30], the use as a heart stimulating agent by Johann Wansleben in 1673, the effect on stomach aches and vomiting by Olfert Dapper in 1688, the chewing in order to assist digestion, teeth whitening and improvement of mouth odor by Vincenzo Coronelli in 1696, the use of tooth-picks by mastic tree wood for strengthening of the teeth by Aubry de la Motraye [31].

Mastic was also present in many European pharmacopoeias of the 19th century, as the "Hellenic Pharmacopeia" (Smyrna 1835) and its numerous prescriptions for ointments and pills containing mastic. British pharmacopeias as "Pharmacopoea Edinburgensis" (1813) mentioned the disinfectant, stimulating and sweetening properties of mastic. The Belgian "Manuelle de Matière Médicale" (1839) underlined the use of mastic in numerous preparations against catarrh and diarrhea and also for *Spiritus Mastiches Compositus*, which was frequently present in other European pharmacopoeias [32].

French pharmacopoeias of that period, as those of "Pharmacologis Seu Materia Medica" in 1803 and "Traité complet de Pharmacie théorique et pratique" in 1833, mentioned mastic as a compound of several preparations, as *Pilulae amarocatharticae* against dyspepsia, in *Tincturia vulneraria simplex* against skin injuries, in *Liquor odontalgicum* as analgesic for teeth extraction, in *Poudre de Mastique, Tincture éthérée de mastique, Mastic dentaire* etc. Numerous German pharmacopoeias, as "Pharmacopoeia Hassiae electoralis", "Pharmacopoea in usum nosocomis militaris Wurcenburgensis", "Pharmacopeia Badensis" and others, referred to mastic and its uses, usually as an analgesic, in dentistry and for plasters, usually for military applications. Also, in Italian pharmacopoeias as "Pharmacopoea Taurinensis", "Farmacopoea Ferrarese", "Farmacopoea Teorica-Pratica" etc, mastic is mentioned as a diuretic and as a compound of *Mastix pro dentibus*, for use as a temporary tooth sealing [32].

Modern Times

After the liberation of Chios by the Greek fleet in 1912, the state tried to organize matters concerning mastic production and distribution. In order to release farmers from exploitation by mediators, the government passed the law for obligatory association of all mastic producers and the creation of Chios Gum Mastic Growers' Association (CGMGA), the sole agency competent for collecting, packaging and trading of mastic sold to it by the growers. This form of organization helped mastic production grow, fortified the growers' income and gave the opportunity for a co-ordinated promotion of mastic on an international level, together

with co-operation with academic researchers on the way of revealing and substantiating mastic's therapeutic properties.

STUDIES OF THE BIOLOGICAL ACTIVITIES OF MASTIC & MASTIC OIL

Mastic in the Treatment of Gastrointestinal Disorders

The healing properties of mastic, especially those related with the gastrointestinal system, were preserved in the traditional therapeutics of the peoples of Eastern Mediterranean and Middle East, among which the use of mastic is quite widespread, and are still being practiced. The therapeutic uses of mastic gave the initiative for the first studies on the activity of mastic against ulcer and gastritis in the middle 1980's. The first study to present results on clinical patients with active symptoms of endoscopically detected duodenal ulcer after mastic administration was that of Al Habal *et al* in 1984 [1]. According to this double-blind clinical trial, 80% of the patients receiving mastic (study group) reported a relief from the symptoms, against to 50% of those receiving placebo. These more or less subjective statements were enforced by sequential endoscopic examination, according to which healing was detected in 70% of the study group, as opposed to only 22% of the placebo group, pointing to a statistically important difference ($P<0.01$).

Shortly after, Al-Said *et al* showed that orally administered mastic reduced the degree of gastric mucosa damages in mice suffering by gastric or duodenal ulcer considerably [2]. Pathogenesis was caused either mechanically (pyloric constriction), chemically (administration of 50% ethanol), or pharmaceutically (administration of aspirin, phenylbutazone or reserpine), or by stress because of fasting.

The mice were receiving one oral dose of 500 mg of mastic/kg of body weight. After the examination of stomach and duodenum and the estimate of damages depending to their size and heaviness, it was found that oral administration of mastic reduced the degree of gastric mucosa damages considerably. In addition, free acidity was observed in mice that had undergone six hours of pyloric constriction, and an intense cytoprotective effect of mastic was revealed in those that had received 50% ethanol. The results suggested that the anti-ulcer effect of mastic could be attributed to its mild anti-secretive and local cytoprotective activities. The fact that ulcer was caused by a variety of factors (pyloric constriction, administration of 50% ethanol, aspirin, phenylbutazone or reserpine, stress due to fasting) made the experiment conditions resemble to the actual diversity of potential causes of ulcer. These two studies gave the first measurable proof for mastic's healing effect on duodenal ulcer for both human patients [1] and mice [2].

In a more recent study [33], the effect of mastic oil in reducing the intestinal damages induced by diclofenac and the bacterial translocation in mice, a phenomenon caused by non-steroid anti-inflammatories in general, were investigated. After estimating all the parameters that are increased by diclofenac administration, it was found that they were all reduced by administration of 1.0 mg of mastic oil/kg of body weight.

In a recent study [34], Dabos *et al* showed that administration of mastic to patients suffering by functional indigestion for three weeks induced relief of symptoms for 77% of the patients, as opposed to 40% of those receiving placebo. It was the first study concerning the effect of mastic in functional indigestion.

Anti-*H. pylori* Activity

All the studies mentioned above showed that mastic as well as mastic oil exhibit activity upon gastrointestinal disorders. After Warren and Marshall discovered *Helicobacter pylori* in 1983 [35] and correlated it with gastric diseases, the interest in determining the mechanism of action of mastic and mastic oil in these diseases was focused on the investigation of their anti-*H.pylori* properties. Numerous studies were carried out, concerning both *in vitro* experiments and clinical trials in the context of revealing the effect of mastic in confronting *H.pylori* and the disorders caused by it. The necessity of such a research was accentuated by the need for alternative, non-antibiotic therapies for infectious diseases such as ulcer, because of the emerging of multiple pathogenic microorganisms resistant to antibiotics and the potential threat they constitute for public health [36].

The first study mentioning anti-*H.pylori* activity of mastic was published in *New England Journal of Medicine* in 1998 [3]. It revealed the bactericidal activity of mastic upon *H.pylori in vitro* at concentrations as low as 60 μg of crude mastic per millilitre of broth culture. Lower concentrations were proven inhibitory for the growth of the bacterium, and transmission electron spectroscopy revealed ultrastructural changes in the bacteria. The results clearly showed the antibacterial activity of mastic against *H.pylori* and therefore offered a possible explanation of its anti-ulcer effect, by ratifying the previous references on mastic's healing effect on ulcer and potentially explaining its therapeutic effect on patients suffering by gastrointestinal diseases.

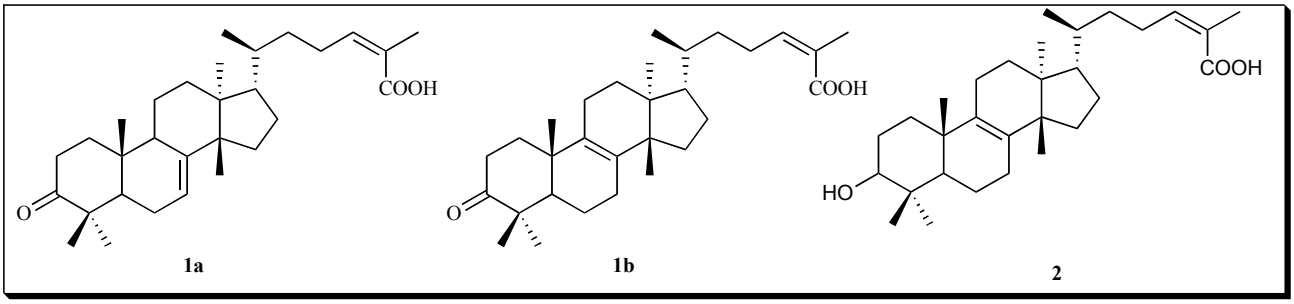
Studies that followed [37, 38], assessed the antibacterial activity of mastic upon isolated clinical strains of *H.pylori* in concentrations from 1.9 to 2000 μg/ml. The calculation of the Minimum Bactericidal Concentrations (MBC's) by the microdilution method, showed that mastic exhibited considerable bactericidal effect upon the 12 *H.pylori* strains isolated from patients that were used, by killing 50% of the bacteria at a concentration of 125 μg/ml, and 90% at a concentration of 500 μg/ml. In addition, microscopic observance of the morphology of the bacterium by electron emission revealed air bubble release, abnormalities in morphology and segmentation of *H.pylori* cells. Although the concentration required was higher than that stated by Huwez *et al*, the bactericidal activity was now extended to a larger number of strains, and a mastic concentration of 125 μg/ml was nevertheless found to be killing 50% of the bacteria. Moreover, the observance of structural effects of mastic on *H.pylori* cells could offer some explanation on the mechanism of mastic's anti-*H.pylori* activity.

In a more recent study [39], it was discussed whether the anti-*H.pylori* activity of mastic could be attributed to the arabinogalactan-proteins (AGP's) isolated by mastic after extraction by aqueous solution of NaCl and Tris-HCl at a pH 7.5. The growth of *H.pylori* cells in the presence of mastic aqueous extracts containing AGP's was studied, and the results showed that the viability of the bacterium was affected, by obstruction of its growth. There were no indications whether AGP's were responsible for causing morphological abnormalities in *H.pylori*, as it was mentioned for total mastic [38]. This was a first approach to the investigation of the constituents of mastic potentially responsible for the anti-*H.pylori* activity of the gum.

Following the study above mentioned, Kottaki *et al* [40] investigated the effect of AGP's, both *in vitro* and *in vivo*, on the innate cellular immune effectors (neutrophils activations) comparing *H.pylori*-infected patients and healthy controls receiving 1 g of mastic daily for two months, under the presence of *H.pylori* neutrophil-activating protein (*HP*-NAP). It was found that AGP's inhibit neutrophil activation in the presence of HP-NAP.

In 2003, two studies carried out by the same research group questioned the capability of mastic to eradicate *H.pylori* from both mice [41] and human patients [42]. Mastic was administered alternatively to a triple eradication scheme to the subjects of each study for periods of 7 and 14 days respectively.

In the first study [41], the susceptibility of *H.pylori* SS1 strain to mastic was assessed by determination of the Minimum Inhibitory



Concentration (MIC) and the MBC values, found to be 7.80 and 31.25 mg/L respectively. Then, an *H.pylori* SS1 strain suspension was administered endogastrically to the mice study group, alternatively with plain brain-heart infusion agar for the control group. Four weeks after infection, 0.86 mg of mastic diluted in ethanol (roughly equivalent to 2 g for human subjects), or a triple therapeutic scheme consisting of metronidazole, clarithromycin and omeprazole was administered to mice twice daily for a seven-day period. After removal, homogenization and cultivation of the stomachs in order to detect *H.pylori* presence, it was found that the triple scheme eradicated the infection in 19 out of 20 mice, while mastic showed a complete failure (0 out of 18 mice, $P<0{,}001$). No statistically significant reduction of the bacterial load in mastic-treated mice was detected, either.

The researchers reached to the conclusion that mastic was not competent to eradicate *H.pylori* infection from mice by itself. The study excluded neither the case of synergistic action of mastic with other factors nor the possibility of insufficient absorption and release of mastic and its compounds inside the stomach of mice, probably due to inherent differences between humans and mice in relation to the effect of mastic. One possible explanation given about the beneficial effects of mastic on humans is its cytoprotective and antisecretive activities, as mentioned by Al-Said *et al*. [2].

In the second study [42], it is examined whether mastic gum can either suppress or eradicate *H.pylori* infection from humans. Nine *H.pylori* positive human subjects with no duodenal ulcer were subjected to treatment with 1 g of mastic four times daily for 14 days. [^{13}C]Urea breath tests (UBTs) were carried out right before, on the 15th day and five weeks after the treatment.

Mastic had no effect on *H.pylori* status for none of the eight subjects that completed the treatment. They were all found positive to the bacterium with the urea breath test to which they were submitted, both immediately after completion of the administration and five weeks later.

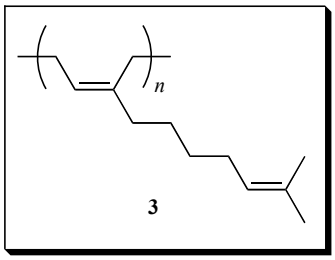
The researchers regarded that even large doses of mastic had no significant clinical effect on *H.pylori* in humans, while they also questioned the validity of a previous study [1] according to which mastic could be beneficial in ulcer treatment, since the credibility of the experiment was not sufficiently documented, according to Bebb *et al*.

The study reached the conclusion that *H.pylori*-related ulcer therapy should only be conducted by antisecretory drugs and eradication schemes, since they constitute the only possible way to cure ulcer and prevent relapse. It is quite interesting, however, to note that one of the researchers has participated in the past in clinical trials funded by the manufacturer of a known proton pump inhibitor, as it stated at the end of the paper.

In 2007, the anti-*H.pylori* activity of mastic was justified by a study of our laboratory [23], which particularly examined the extracts and pure major constituents of mastic gum for their potential activity against *H.pylori*. A total mastic extract without polymer (TMEWP) was prepared after removal of the contained insoluble polymer in order to ameliorate solubility and enhance in vivo activity. Administration of TMEWP to SS1-mice infected by *H.pylori* over a period of 3 months with an average dose of 0.75 mg/day led to an approximately 30-fold reduction in the *H.pylori* colonization (1.5 logCFU/g of tissue). No attenuation was observed, however, in the *H.pylori*-associated chronic inflammatory infiltration and the activity of chronic gastritis. In order to determine potential active mastic constituents, the TMEWP was fractionated into an acidic and a neutral fraction. The structures of the major components contained within each fraction were extensively characterized by NMR and MS spectroscopy. After further chromatographic separation, the acidic fraction gave mainly the major triterpenic acids, while the neutral fraction gave several triterpenic alcohols and aldehydes. The two mastic fractions and isolated pure triterpenic acids were tested for in vitro activity against 11 *H.pylori* clinical strains. The most active extract was found to be the acidic fraction (MBC 0.139 mg/ml), the major compounds of which are masticadienonic (**1a**) and isomasticadienonic acids (**1b**), and the most active pure compound was isomasticadienolic acid (**2**, MBC 0.202 mg/ml, 0.443 mM). The results of our research showed that administration of TMEWP may be effective in reducing *H.pylori* colonization and that the major triterpenic acids in the acidic fraction are possibly responsible for the antibacterial activity. This study could constitute an initiative for further investigation of the role of the acidic compounds of mastic in its anti-*H.pylori* activity.

For additional information on known mastic constituents, see Table **2** for their isolation, as well as their structures at the end of the text.

In a 2009 study about the anti-*H.pylori* effect of mastic [43], mastic polymer (containing mainly *cis*-1,4-poly-β-myrcene, **3**) is mentioned as the most active of its fragments, followed by the acidic fraction and mastic gum itself, whereas the neutral fraction was inactive. The increase in potency for both the polymer after oxidation, and the gum after chewing (mastication) was considerably high (100% and 50%, respectively).



In a recent study by Dabos *et al* [44], different doses of mastic were administered to two groups of patients (A & B) with a detected *H.pylori* infection for 14 days, while a third group (C) received mastic and pantoprazole, and a fourth one (D) was given a triple therapeutic scheme of pantoprazole, amoxicillin and clarithromycin for the same period. Breath urease test showed that the bacterium was eradicated in 4/13 patients in Group A, 5/13 in Group B, 0/13 in Group C and 10/13 in Group D. While the results

were not statistically significant for Groups A and B, they showed a tendency for mastic to eradicate *H.pylori*. The paradox in the failure of mastic-pantoprazole combination could be due to the increase in the pH of stomach caused by proton pump inhibitors, which may lower the potency of mastic's active ingredients, probably responsible for its anti-*H.pylori* activity [23].

Antimicrobial – Antifungal Activity

The discovery of the anti-*H.pylori* effect of mastic followed its already known antimicrobial properties, as mentioned in 1957 by Abdel-Ghaffar *et al* [45], in the first reference of the biological activities of the gum. The initiative for the particular study was the observance that Egyptian villagers exposed earthenware water pitchers to fumes of the burning gum as a means of preventing slime formation. The growth of the slime organism, which was partly identified as a bacterium closely resembling *Bacillus subtilis*, was completely inhibited when culture was attempted in Petri dishes exposed to fumes of burnt resin, but it was not affected when powdered resin was added to the nutrient agar. Fractionation of the fumes by vacuum distillation gave, among others, a fraction (b. 120-50°) that inhibited *B. subtilis*, as well as *Streptococcus faecalis, Staphylococcus aureus, Escherichia coli, Proteus vulgaris,* and *Pseudomonas pyocyanea (P. aeruginosa)*.

The antimicrobial activity of mastic oil is described for the first time by Tassou & Nychas in 1995 [4], as expressed during the process of food spoilage and against food-borne organisms. It was found that addition of mastic oil in broth cultures inoculated with Gram (+) (*S. aureus* and *Lactobacillus plantarum*) and Gram (-) bacteria (*Pseudomonas fragi* and *Salmonella enteridis*) in concentrations from 0.1 to 1.5% v/v inhibited their growth, as monitored by the Malthus 2000 apparatus. The inhibitory effect was greater on Gram positive bacteria than on negative. In most cases the size of inoculum and the concentration of mastic oil affected the growth and/or survival of the organisms.

The study of Ali-Shtayeh *et al* [46] attributed antifungal activity to the aqueous extract of mastic, which was found to be active against *Microsporum canis, Trichophyton mentagrophytes* & *Trichophyton violaceum*, by decreasing their colonies' growth from 36% to 100%.

In a study examining the chemical composition of mastic oil together with that of the essential oils of the leaves and twigs of *P. lentiscus* var. *chia*, Magiatis *et al* [5] also examined the antimicrobial and antifungal activities of mastic oil, total mastic extract and acidic and neutral mastic fractions against six bacteria (*S. aureus, Streptococcus epidermidis. P. aeruginosa, Enterobacter clocae, Klebsiella pneumoniae & Escherichia coli*) and three fungi (*Candida albicans, C. tropicalis & Torulopsis glabrata*), with mastic oil proven to be the most active.

In 2005, Koutsoudaki *et al* [47], while analyzing the chemical composition of mastic and mastic oil, also examined the antimicrobial activity of mastic oil and its major fractions and compounds using the disk diffusion method. Fragmentation of mastic oil, which was carried out in order to get a better picture of the components responsible for its antibacterial activity, led to the identification of several trace components. Each of the minor compounds exhibited different grades of activity against different bacteria. This variety showed that the antimicrobial efficacy of mastic oil cannot be easily attributed to one or some of its compounds, and should be considered as a result of synergy between numerous or even all of its components.

Antioxidant Activity

Mastic, as well as other resins, has been used for centuries as a preservative for fats and oils by various peoples. Such a use by Egyptian villagers triggered the first study on mastic's antioxidant activity by Egyptian researchers in the 70's. Abdel-Rahman *et al* [6] showed that mastic possessed antioxidant activity similar to that of butylated hydroxyanisol. The same group [48] showed antioxidant activity of mastic for cottonseed oil and sunflower oil similar to that of BHA and Embanox B, with 0.05 to 0.1% of mastic being adequate for temperatures from 25 to 45^{o}C.

In 2003, Andrikopoulos *et al* [49] tested the potential protective effect of several resins upon the copper-induced oxidation of human low-density lipoprotein (LDL), rating the hydromethanolic extract of mastic as the most active. Several combinations of triterpenes, including mastic compounds such as oleanolic acid, showed considerable protective activity as well.

Assimopoulou *et al* [50] studied mastic together with other resins for their antioxidant activity *in vitro*, using lard, corn oil and sunflower oil as oily substrates. Mastic as well as mastic oil showed considerable activity, and it is stated that they could both be used as preservatives in pharmaceutical and cosmetic preparations, as well as for functional foods.

Hypolipidemic Activity

Recently, and possibly because of the studies attributing antioxidant activities to mastic [49, 50], two Greek research groups examined the hypolipidemic activity of mastic. The first one [7] studied the molecular mechanism through which the total polar extract of mastic inhibits the cytotoxic effect of oxidized LDL (oxLDL) on peripheral blood mononuclear cell (PBMC), which underwent apoptosis and necrosis when exposed to oxLDL, dependent on the duration of exposure. Inhibition of both the phenomena was observed when culturing cells with oxLDL and the polar extract concurrently. The levels of intracellular antioxidant glutathione (GSH), as well as the expression of CD36, a class B scavenger receptor, on CD14-positive cells, were measured. CD36 has been identified as the oxLDL receptor in macrophages and may play a pivotal role in atherosclerotic foam cell formation. The results showed that oxLDL decreased GSH levels and upregulated CD36 expression, while mastic total polar extract restored GSH levels and downregulated CD36 expression, even at the mRNA level.

In order to reveal the biologically active constituents of the resin's polar extract, fractions derived from RP-HPLC analysis were examined for their antioxidant effect on oxidatively stressed PBMC. The triterpenoid fraction revealed remarkable increase in intracellular GSH. It is suggested that GSH restoration and downregulation of CD36 mRNA expression are the pathways for mastic triterpenes to exert their antioxidant/antiatherogenic effect.

In the second study [8], the effect of mastic on cardiologic and hepatic biochemical indices of humans was assessed. 133 subjects aged over 50 were randomly assigned to two groups, the first (high-dose group) ingesting daily 5 g of mastic powder and the second receiving daily a mastic solution (low-dose group). Serum biochemical parameters were determined on a monthly basis for an 18-month (first group) and a 12-month (second group) follow-up period.

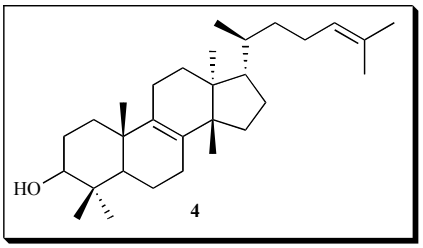
The first (high-dose) group exhibited a decrease in serum total cholesterol, LDL, total cholesterol/HDL ratio, lipoprotein, apolipoprotein A-1, apolipoprotein B (apoB/apoA-1 ratio did not change), SGOT, SGPT and gamma-GT levels. In the low-dose group, glucose levels decreased in male subjects. The results indicate that Chios mastic powder could have a hepatoprotective/cardioprotective role *in vivo* in humans.

Anti-Inflammatory Activity

Complementary to the study of mastic's hypolipidemic activity in the aim of describing its potential cardioprotective role, came

two recent studies of its anti-inflammatory activity. In 2009, Zhou *et al* [9] showed that mastic inhibited the production of pro-inflammatory substances such as nitric oxide (NO) and prostaglandin ($PG)E_2$ in lipopolysaccharide (LPS)-activated mouse macrophage-like RAW264.7 cells, leading to the decline of viable cell number. It was determined by western blot and RT-PCR analyses that mastic acted by inhibiting the expression of inducible NO synthase (iNOS) and cyclooxygenase (COX)-2 at both protein and mRNA levels.

The anti-inflammatory activity of mastic was further studied by Loizou, Paraschos *et al* in 2009 [10]. In particular, they examined the anti-inflammatory activity of Mastic Neutral Fraction (MNF) in human aortic endothelial cells. The attachment of leukocytes to the vascular endothelium and the subsequent migration of cells into the vessel wall are early events in atherogenesis, and this process requires the expression of endothelial adhesion molecules. Therefore, the effects of MNF (in concentrations 25-200 μg/ml) and tirucallol (**4**, one of its major compounds possessing a phytosterolic structure, 0.1-100 μM) on the expression of adhesion molecules (VCAM-1 and ICAM-1) and the attachment of monocytes (U937 cells) in TNF-α stimulated Human Aortic Endothelial Cells (HAEC) were studied. The methods used to investigate these effects were Cell ELISA for MNF and Adhesion assay for tirucallol. Both MNF and tirucallol inhibited significantly VCAM-1 and ICAM-1 expression in TNF-α-stimulated HAEC. They also inhibited significantly the binding of U937 cells to TNF-astimulated HAEC and attenuated the phosphorylation of NFkB p65.



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Another aspect of mastic's anti-inflammatory potential was studied in 2007 by Kaliora *et al* [11], who evaluated the effectiveness of mastic administration on the clinical course and plasma inflammatory mediators of patients with active Crohn's disease (CD). A significant reduction of CD activity index, plasma interleukin-6 levels and C-reactive protein levels were measured after treatment with mastic, while total antioxidant potential was increased and no signs of side effects were observed. The same research group [12] assessed the effects of mastic administration on cytokine production of circulating mononuclear cells of patients with active CD. The results showed a reduction of tumor necrosis factor-alpha (TNF-α) secretion, and also a significant increase in the macrophage migration inhibitory factor (MIF), indicating that random migration and chemotaxis of monocytes/macrophages was inhibited. The conclusion of the study was that mastic acted as an immunomodulator on peripheral blood mononuclear cells, providing strong evidence that it might be an important regulator of immunity in CD.

Anticancer Activity

There are several studies concerning the anticancer activity of mastic. Prostate [15, 16, 17] and colorectal cancer [13, 14] are among the ones upon which the effect of mastic has been studied more extensively, as well as leukemia [52] and lung carcinoma [53].

Activity Against Prostate Cancer

In 2006, He *et al* [15] showed that mastic affects the function of prostate cells androgen receptors, by inhibiting *in vitro* the receptor's expression both on the m-RNA and the protein level, thus setting the bases for the hypothesis of mastic's potential prostate anti-cancer activity.

In 2007, the same research group [17] initially studied the effect of mastic on the proliferation of androgen-independent prostate cancer PC-3 cells, and reached the conclusion that it inhibits the proliferation and blocks the cell cycle progression in PC-3 cells by suppressing NF-B activity and the NF-B signal pathway. Furthermore, they studied whether mastic could regulate the expression of maspin, a prostate tumour suppressive protein of prostate cancer cells [16]. The research showed that mastic induces the expression of maspin, both on the m-RNA and the protein level. It is concluded from the above studies that mastic could constitute an important factor against prostate cancer.

Activity Against Colorectal Cancer

Balan *et al* [13] showed in 2005 that a hexane extract of mastic induced apoptosis in HCT116 human colon cancer cells *in vitro* through a caspase-related mechanism.

As a continuation of the above mentioned study, Balan *et al* [51] demonstrated that a 50% ethanol extract of mastic also inhibited proliferation and induced death of HCT116 human colon cancer cells *in vitro*, possibly through a caspase-related mechanism, which nevertheless remained unclear.

The *in vivo* activity of the hexane extract of mastic was tested against human colon tumour in immunodeficient mice by Dimas *et al* [14]. The results showed that mastic hexane extract administered at a dose of 200 mg/kg daily for 4 consecutive days (followed by 3 days without treatment) inhibited tumour growth by approximately 35% in the absence of toxicity (side-effects) after 35 days. It was thus indicated that mastic possesses antitumor activity against human colorectal cancer under the experimental conditions of this study.

Antileukemic Activity

In 2006, Loutrari *et al* [52] showed that mastic oil (concentration and time dependently) exerted an antiproliferative and proapoptotic effect on human K562 leukemia cells and prevented K562 and B16 mouse melanoma cells from releasing vascular endothelial growth factor (VEGF); moreover, it inhibited endothelial cell (EC) proliferation without affecting cell survival and decreased significantly microvessel formation both *in vitro* and *in vivo*.

Activity Against Lung Carcinoma

In order to investigate molecular mechanisms potentially triggered by mastic oil, Moulos *et al* [53] treated Lewis Lung Carcinoma (LLC) cells with mastic oil or DMSO and RNA was collected at distinct time points. Microarray expression profiling was performed, as well as RT-PCR validation for selected genes in LLC cells and three different human cancer cell lines. It was demonstrated that mastic oil caused a time dependent alteration in the expression of 925 genes, many of which are associated with several biological processes and functions. Certain modifications, for instance those on cell cycle/proliferation, survival and NF-κB cascade, indicated the anti-proliferative, proapoptotic and anti-inflammatory effects of mastic oil. The expression profiles of certain genes were similarly altered by mastic oil in the majority of test cancer cell lines. It was concluded that microarray gene expression profiling combined with bioinformatic analyses on a model of mouse lung adenocarcinoma provided evidence on mastic oil inhibitory actions on tumour cell growth and survival, constituting this study as the first one addressing the mechanisms of action of mastic oil at genome-wide gene expression level and upon specific target molecules and pathways.

Table 2. Compounds Isolated from Mastic with Corresponding References and Formulas

Compound	Reference no	Formula
masticadienonic acid	[58], [23]	1a
isomasticadienonic acid	[59], [23]	1b
oleanonic acid	[59], [23]	5
moronic acid	[23]	6
masticadienolic acid	[23]	7
isomasticadienolic acid	[23]	2
tirucallol	[58], [23]	4
oleanonic aldehyde	[23]	8
oleanolic aldehyde	[23]	9
3-oxo-28-norolean-12-ene	[60], [23]	10
20(*S*)-3β-acetoxy-20-hydroxydammara-24-ene	[60]	11
3-oxo-dammara-20 (**21**),24-diene	[60]	12
3β-hydroxymalabarica-14 (**26**),17*E*,21-triene	[60]	13
3-oxomalabarica-14 (**26**),17*E*,21-triene	[60]	14
3β-hydroxy-28-norolean-12-ene	[60]	15
3-oxo-28-norlup-20 (**29**)-ene	[60]	16
(8R)-3-oxo-8-hydroxy-polypoda-13*E*,17*E*,21-triene	[60]	17
1,4-poly-β-myrcene	[61]	3
tyrosol	[62]	in traces
p-hydroxy-benzoic acid	[62]	
p-hydroxy-phenylacetic acid	[62]	
banillic acid	[62]	
gallic acid	[62]	
trans-cinnamomic acid	[62]	

Allergenic Activity

The sole references of any allergenic activity of mastic are those of Lee T.Y. *et al* [54] and Wakelin [55], both related to allergic contact dermatitis caused to three patients in the former case and one in the latter. Lee T.Y. *et al* reported contact dermatitis due to a Chinese herbal orthopaedic solution (Tieh Ta Yao Gin), which contains, among others, mastic as an analgesic and anti-inflammatory agent. Wakelin mentioned florid blistering dermatitis after post-operative application of compound mastic paint (a 40% mastic preparation used to protect wounds and make dressings adhere). In both cases, patch testing demonstrated allergy to mastic.

Toxicity

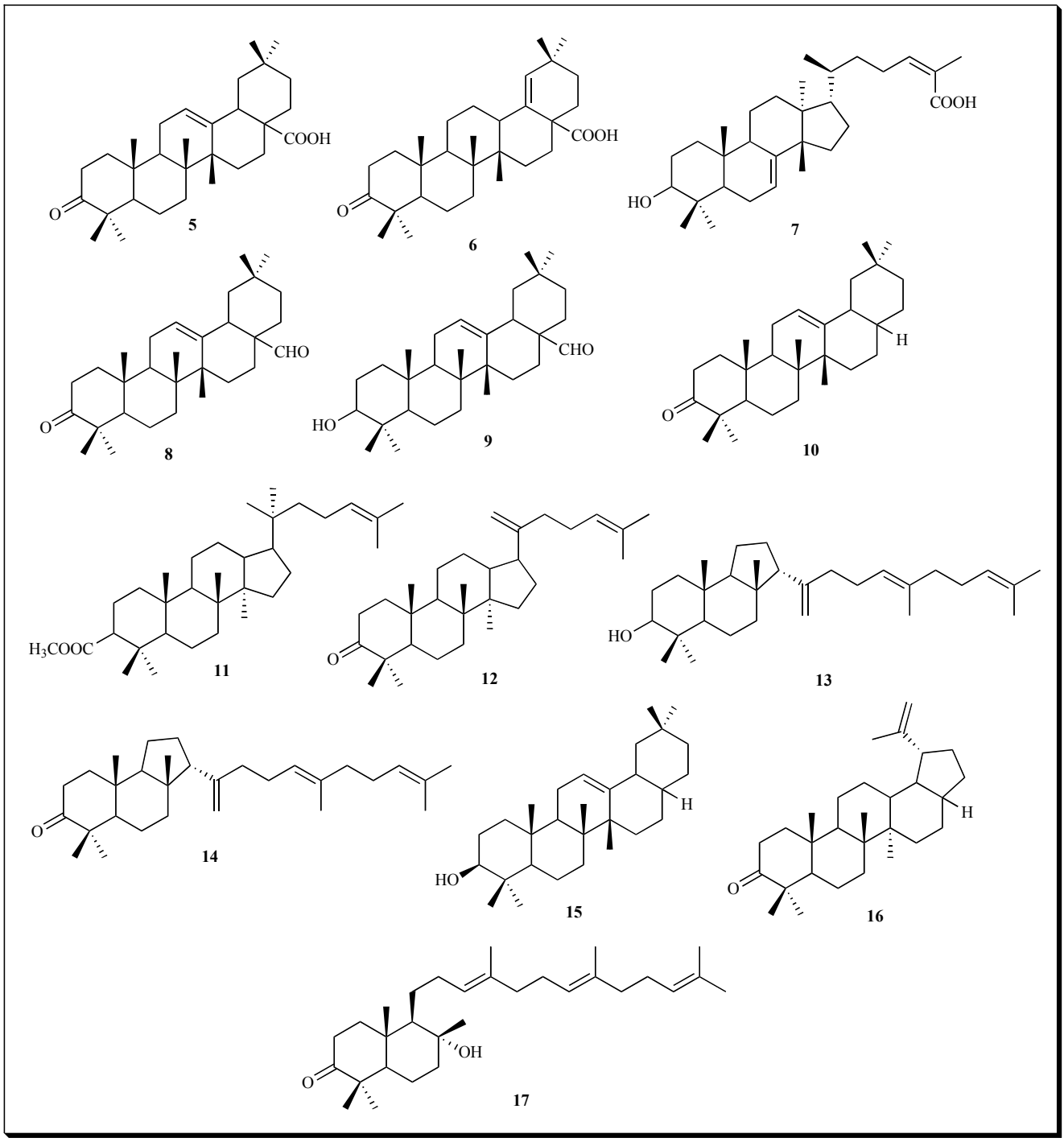
There are certain references on mastic's toxicity on animals, specifically related with its toxic effects on the liver. In one case [56], mastic was added in four different proportions (up to 2%) to the diet of F344 rats for 13 weeks. Although no mortality or obvious clinical signs were observed in any of the animals, body weights were significantly reduced in the high dose-treated group, while absolute and relative liver weights were increased in a dose-related manner. Additionally, a series of hematological parameters as well as serum biochemistry parameters were altered (e.g. an increase in white blood cell and platelet count, an increase in total proteins, albumin, and total cholesterol). However, no gross lesions were revealed at necropsy macroscopically, nor were any treatment-related findings in the organs examined detected microscopically. The conclusion drawn was that mastic administration has a no observed adverse effect level (NOAEL) of 0.67% in the diet of rats.

In a more recent study [57] the modifying effects of Chios Mastic Gum on rat liver carcinogenesis were investigated. F344 rats were subjected to the established rat liver medium-term carcinogenesis bioassay (Ito-test) by intraperitoneal injection of diethylnitrosamine (DEN). Two weeks later, mastic was added in the animals' diet in four different proportions (up to 1%), partial hepatectomy followed, and the experiment was terminated at week 8 The results showed a significant dose dependent increase in liver weight, together with an increase in parameters related with the formation of preneoplastic lesions in the liver, such as glutathione S-transferase placental form (GST-P)-positive cell foci and 5-Bromo-2′-deoxyuridine (BrdU)-labeling indices. This study displayed a promotion potential of mastic on the formation of preneoplastic lesions in the established rat liver medium-term carcinogenesis bioassay.

A synopsis of the biological activities of gum mastic, its fractions and compounds is given in Table **1**.

CONCLUSIONS

Mastic has been the subject of various studies, together with its extracts and its compounds, concerning their biological activities. The effect of mastic on gastrointestinal disorders and mainly its anti-*H.pylori* activity have been the main targets of most of the researches. The result of this series of scientific work was the verification of the positive role of mastic in the treatment of ulcer [1, 2, 3, 23, 33, 37, 38] and indigestion [34]. Additionally, the anti-*H.pylori* activities of some of its compounds were revealed (inhibition of the colonization of the bacterium [23] by acidic



fraction and isomasticadienolic acid, **2**, obstruction of its growth by arabinogalactan-proteins [39] and mastic polymer, **3** [43]). Furthermore, and as a complement of its gastrointestinal activity, mastic has been proven to possess anti-Crohn's disease properties [11, 12]. Its role as an anti-inflammatory agent has been further supported by the discovery of its inhibition in the production of pro-inflammatory substances [9] and its anti-inflammatory activity in human aortic endothelial cells, mainly focused on its neutral extract and the phytosterolic compound tirucallol, **4** [10]. These activities, combined with its antioxidant [49, 50] and its hypolipidemic properties [7, 8], can potentially lead to the hypothesis for its cardioprotective activity. Furthermore, recent researches attributing anti-cancer potential to mastic [13, 14, 15, 16, 17, 52, 53], together with clinical studies confirming its anti-indigestion [34] and anti-ulcer effect [43] on human subjects, have established mastic as a valuable therapeutic agent. The role of mastic as a natural source of biologically active compounds remains to be clarified by additional studies, concerning mainly the acidic compounds, namely the triterpenic acids for their anti-*H.pylori* activity, and its neutral compounds of phytosterolic structure, such as tirucallol, as potential cardioprotective agents.

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