ΕΝΩΣΗ
ΜΑΣΤΙΧΟΠΑΡΑΓΩΓΩΝ ΧΙΟΥ
THE CHIOS GUM MASTIC
GROWERS ASSOCIATION

OVERVIEW OF THE MAJOR SCIENTIFIC PUBLICATIONS ON THE BENEFICIAL ACTIVITY OF CHIOS MASTIHA

SCIENTIFIC NAME: ***Pistacia lentiscus Var. Chia***

2019 / EXTENDED VERSION

ΕΝΩΣΗ ΜΑΣΤΙΧΟΠΑΡΑΓΩΓΩΝ ΧΙΟΥ
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80 XPONIA YEARS

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introduction

It is without a doubt, that since the ancient era Chios Mastiha (Mastic Gum)* has strongly shaped the identity of the fragrant island of Chios, which lies in the Aegean Sea, in the Eastern sea border of Greece.

The plant belongs to the *Pistacia Lentiscus* L. specie of the Anacardiaceae family. It is an evergreen shrub, extensively spread in the Mediterranean region. The unique cultivar of *P. Lentiscus cv chia* is exclusively cultivated in Southern Chios (Mastihohoria).
The distinctive white to yellowish, semitransparent, natural resin of the Mastiha plant, shows the properties of opaque crystals and is characterized by a balsam like odour. Also known as the *'tear of Chios'*, it is obtained as an extract, after causing incisions on the tree trunk and on the larger branches with special sharp instruments. It exudes in droplets onto the ground, and whilst it is flowing, it is a gummy, clear liquid. After approximately 15-20 days pass, it solidifies in irregular shapes. Following harvesting, the commodity is placed into wooden boxes and it is stored in cool places, where it shall be diligently cleaned in order to be finally delivered to Chios Mastiha Growers Association.

The biological activities of Chios Mastiha is being attributed to various compounds. The components which might contribute to its therapeutic effects belong to the class of mono- and sesquiterpenoids (Barra et al, 2007) and triterpenoids (f.i. masticadienonic acid) (Assimopoulou and Papageorgiou 2005). Apart from the above, approximately 25% of its total weight is a polymer, which in an acid environment becomes a runny resin that could have cytoprotectant effects in patients (Dimas et al, 2009). In total, more than 70 components have already been isolated from pure Chios Mastiha (Kaliora et al, 2004).

Interestingly, Chios Mastiha has been reportedly used in traditional Greek medicine relieving the diverse gastrointestinal disorders, such as abdominal pain, dyspepsia, gastritis and peptic ulcer for more than 2.500 years. More precisely, Hippocrates, Dioscorides and Galenos, among other Ancient Greek physicians, cited its properties and recommended its use.

The extraordinary uses and trade of Chios Mastiha continued in the Byzantine and Medieval period, and during the occupation of Chios island by the Genovese, Mastiha met an exceptional prosperity by being spread to the Islamic world and through fruitful exports to Europe. Mastiha afforded countless privileges to the island and to the locals during the Ottoman period, most importantly the reduced tax rates.

Nowadays, it is used as a seasoning in Mediterranean cuisine, in the production of chewing gum, in perfumery, in dentistry, and for the relief of epigastric pain and protection against peptic ulcer. It is of vital importance to mention that solid scientific evidence is constantly being produced regarding the therapeutic activity of Chios Mastiha. Its gastro-intestinal, antioxidant, anti-inflammatory, antidiabetic, antimicrobial, and anticancer activity, as well as its beneficial effects in oral hygiene and in skin care are firmly documented in the international medicinal scientific journal.

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* The designation "Chios Mastiha" is being adapted to the delivery destination receiving various alternations like Mastic, Gum Mastic, CGM, Mastiha gum etc.

Independent research groups, both in Greece and abroad, continuously set the ground for both the conventional and the state-of-the-art uses of Chios Mastiha, by conducting laboratory research and clinical trials.

Last but certainly not least, regarding the regulatory status of Chios Mastiha across the globe, in 1997, it had been granted as a product with Protected Designation of Origin (PDO) in the European Union (resin, oil, ELMA chewing gum). Additionally, there is a monograph of Chios Mastiha included in the Ayuverdic Pharmacopoeia of India, under the name Rumimastagi (Resin). In 2014, the know-how of cultivating Chios Mastiha on the island of Chios was inscribed on UNESCO's Representative List of the Intangible Cultural Heritage of Humanity. Furthermore, during the same year, Chios Mastiha got a GMP certificate by the National Organization for Medicines (EOF), and an approval statement as a health functional food in Korea (Korea Food and Drug Administration, KFDA). In 2015, it was assigned a European Union herbal monograph as a traditional herbal medicine used in mild dyspeptic disorders, and for the symptomatic treatment of minor inflammations of the skin and as an aid in healing of minor wounds, by the European Medicines Agency (EMA).

In the present booklet, the most significant published studies on Chios Mastiha are briefly developed concerning the aforementioned uses of the resin in the various sites of the human body.

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GASTRO-INTESTINAL ACTIVITY OF CHIOS MASTIHA

The healing activity of Chios Mastiha in the gastrointestinal system is known from antiquity, with medical applications in numerous situations, like gastralgia and digestive ulcers. Reference has been made for Chios Mastiha from physicians, as well as from pharmaceutical documents of the ancient and medieval eras introducing it as an efficient and advantageous agent for treating gastrointestinal disorders and diseases. Chios Mastiha has been used for centuries in Arab countries among others as a breath sweetener, as a food and drink ingredient, and from traditional healers for upper abdominal pain and discomfort. Owing to its spread in this part of the globe, the first scientific investigations commenced in universities and institutions thereto. Additionally since the 1990's, international and local scientific studies have been significantly augmented and published in prestigious scientific journal, targeting the use of Chios Mastiha against problems relevant to the digestive system. Investigations ceaselessly go on, leading to remarkable findings.

The first double-blind clinical trial took place in 1984. Precisely, 38 patients with symptomatic and endoscopically proven duodenal ulcer participated in a trial aiming at comparing the response to Chios Mastiha (1g per day, 20 patients) and placebo (lactose, 1g per day, 18 patients) orally administered for over 2 weeks. A percentage of 80% of the patients on Chios Mastiha experienced alleviation from the relevant symptoms, compared to 50% of the placebo. Additionally, 70% of Chios Mastiha patients posed endoscopically proven healing, in comparison with 22% of the other group's patients. Chios Mastiha did not cause any side effects. To conclude, Chios Mastiha possesses an ulcer healing activity[1].

Al-Said et al (1984) studied the effect of Chios Mastiha on experimental gastric and duodenal ulcers. Chios Mastiha orally ingested in rats at 500mg/kg remarkably decreased the intensity of gastric mucosal damage. Moreover, Chios Mastiha administartion caused a notable reduction of free acidity and a marked cytoprotective activity. Interestingly, the protective action was absent in intraperitoneal administration. A mild antisecretory and a localized adaptive cytoprotectant effect might be responsible for its anti-ulcer activity[2].

In 1997, Gabr investigated co-precipitates and physical mixtures of indomethacin, lactose and Chios Mastiha in rats, aiming to approach Chios Mastiha's activity on drug dissolution rate, bioavailability and ulcerogenic activity. The preparations were administered orally. Interestingly, Chios Mastiha delayed drug dissolution rate. Regarding bioavailability, the findings indicate a sustained activity of drug from indomethacin- Chios Mastiha physical mixture and coprecipitate, and the ulcerogenic effect of indomethacin decreased in all preparations that included Chios Mastiha[3].

In 1998, Huwez et al used *H. pylori* strains NCTC 11637 and six fresh clinical isolates (three were sensitive and three were resistant to metronidazole). Chios Mastiha was prepared as a stock solution in ethanol at a concentration of 50mg/ml and was diluted in the broth

1. Al-Habbal M.J., Al-Habbal Z., Huwez F.U. [1984]: A double-blind controlled clinical trial of mastic and placebo in the treatment of duodenal ulcer. *Clin Exp Pharmacol Physiol.*, 11 (5): 541-544.
2. Al-Said M.S., Ageel A.M., Parmar N.S., Tariq M. [1984]: Evaluation of mastic, a crude drug obtained from Pistacia Lentiscus for gastric and duodenal antiulcer activity. J Ethnopharmacol., 15 (3): 271-278.
3. Gabr K.E. [1997]: Influence of indomethacin-mastic combinations on dissolution, absorption and gastrointestinal mucosal damage in rats. *Int. J. of Pharm.*, 158: 137–145.

culture which contained 107 cells/ml of H. pylori, for a final concentration from 0.0075 to 1.0 mg/ml. After the incubation, 10-μl aliquots were obtained and placed on agar plates at various times for up to 48 hours. Chios Mastiha killed the *H. pylori* NCTC 11637 strain and the six clinical isolates (reduction in the viable count by a factor of 1000) regardless the organism's susceptibility to nitroimidazoles. The minimal bactericidal concentration at 24 hours for all strains was equal to 0.06 mg of the crude Chios Mastiha per ml. It is worth mentioning that in lower concentrations, the growth of *H. pylori* was still significantly inhibited, with a clear post-antibiotic effect even at the lowest concentration which was used. Furthermore, Chios Mastiha made clear ultrastructural modifications in the bacteria, as demonstrated by transmission electron microscopy. Chios Mastiha exhibits definite antibacterial activity against *H. pylori*, which may partly explain its anti–peptic-ulcer properties, and the analysis of the anti–*H. pylori* activity of the various components of Chios Mastiha may pinpoint the active ingredient[4].

Marone et al (2001) investigated the bactericidal activity of Chios Mastiha against H. pylori against clinical isolates of the bacterium. Chios Mastiha killed 50% of the strains tested at a concentration of 125μg/ml and 90% at a concentration of 500μg/ml. The influence of sub- minimal bactericidal concentrations of Chios Mastiha on the morphologies of *H. pylori* was assessed by transmission electron microscopy. Interestingly, the resin generated blebbing, morphological abnormalities and cellular fragmentation in *H. pylori* cells. To conclude, Chios Mastiha induced fair antibacterial activity against *H. pylori* cells [5].

The objective, in another study conducted in 2001 (Bona et al), was to clarify the bactericidal activity of Chios Mastiha against *H. pylori*. Twelve clinically isolated strains were used. More precisely, 4 strains were susceptible to clarithromycin and metronidazole, 4 strains were resistant to clarithromycin and 4 strains were resistant to clarithromycin and metronidazole. Chios Mastiha killed 50% of the strains tested at a concentration of 125μg/ml while the minimal bactericidal concentration was 90μg/ml. Moreover, the strains susceptible to clarithromycin and metronidazole were inhibited at a concentration of 62.5μg/ml of Chios Mastiha. Thus, Chios Mastiha showed a good antibacterial activity against *H. pylori*. [6]

In 2003, Roe et al examined the activity of Chios Mastiha gum on individuals with H.pylori infected gastritis. Specifically, 48 subjects participated in a double blind clinical trial, who were allocated into two groups, treated with Chios Mastiha or placebo, 3 times daily for 15 minutes, for a total period of 90 days. Researchers concluded that Chios Mastiha has an advantageous effect against *H. pylori* infected gastritis. [7]

Heo et al (2006) focused on investigating whether Chios Mastiha oil may decrease diclofenac induced gut damage and bacterial translocation in rats. The oil demonstrated remarkable protective activity, compared to diclofenac which caused augmentation of the enteric bacterial numbers and bacterial translocation, decreased with Chios Mastiha co-administration. Therefore, Chios Mastiha was proven to exhibit beneficial properties in preventing non-steroidal anti-inflammatory drug induced gut injury and bacterial translocation in rats[8].

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4. Huwez F.U., Thirlwell D., Cockayne A., Ala'Aldeen D.A.A. [1998]: Mastic Gum Kills *Helicobacter pylori*. *N. Eng. J. of Med.*, 339 (26): 1946

5. Marone P., Bono L., Leone E., Bona S., Carretto E., Perversi L. [2001]: Bactericidal activity of *Pistacia Lentiscus* mastic gum against *Helicobacter pylori. J Chemother.*, 13 (6): pp 611-614.

6. Bona S.G., Bono L., Daghetta L., Marone P. [2001]: Bactericidal activity of *Pistacia Lentiscus* gum mastic against *Helicobacter pylori. The Am. J. of Gastroenterol.*, 96 (9) Supplement 1: S49.

7. Roe I.H., Nam S.W., Myung N.H., Kim J.T., Shin J.H. [2003]: The effect of mastic gum on *Helicobacter pylori*-infected gastritis. *Korean J. Gastroenterol.*, 41: 277-283.

8. Heo C., Kim D.W., Do J.H. [2006]: Protective effects of mastic in non-steroidal anti-inflammatory drug induced gut damage and bacterial translocation in a rat model. *Korean J. Med.*, 71: 354-361.

Paraschos et al (2007) examined the *in vitro* and *in vivo* activities of Chios Mastiha extracts and constituents against *H. pylori*. The extracts and pure constituents of Chios Mastiha were investigated with regards to their anti-*H.pylori* effect. A total Chios Mastiha extract without polymer (TMEWP) was prepared after the removal of the insoluble polymer for improving solubility and amelioration *in vivo* activity. The TMEWP was administered to *H. pylori* SS1-infected mice over 3 months. The average dose of Chios Mastiha was equal to 0.75 mg/day and resulted in an approximately 30-fold decrease in the *H. pylori* colonization. Additionally, Chios Mastiha extracts and isolated pure triterpenic acids were tested for their *in vitro* effect against 11 *H. pylori* clinical strains. The acid fraction of Chios Mastiha was proven to be the most active extract (minimum bactericidal concentration 0.139 mg/ml), and the most active pure component was isomasticadienolic acid (minimum bactericidal concentration, 0.202 mg/ml [0.443 mM]). Conclusively, administration of TMEWP may be effective in decreasing *H. pylori* colonization. Furthermore, the major triterpenic acids in the acidic fraction may be responsible for this effect[9].

In 2007, a research group aimed at assessing the effectiveness of Chios Mastiha administration on the clinical course and plasma inflammatory mediators of patients who suffer from active Crohn's disease (CD). The outcome of the study showed that Chios Mastiha significantly reduced the activity index and the plasma levels of nterleukin-6 and C-reactive protein in patients with mildly to moderately active CD[10]. As regards the effect of Chios Mastiha administration on cytokine production of circulating mononuclear cells of patients with active Crohn's disease (CD), Chios Mastiha was shown to act as an immunomodulator inhibiting tumor necrosis factor-alpha (TNF-α) and stimulating macrophage migration inhibitory factor. Although further double-blind placebo-controlled studies in more patients are needed to establish this immunomodulating effect of Chios Mastiha, the present study indicates that Chios Mastiha might be an important regulator of immunity in CD[11].

Kottakis et al (2008) studied arabino-galactan proteins isolated from Chios Mastiha. Trials on the inhibition of growth of *H. pylori* in the presence of the above mentioned proteins, demonstrated that the extracts of at least 1.4 g Chios Mastiha affected the viability of bacteria. The research group suggested that such proteins from Chios Mastiha induce morphologic alterations in *H. pylori* and hence, inhibit its in vitro growth. However, this has to be further explored in live organisms[12].

In 2009 research team investigated Chios Mastiha activity on innate cellular immune effectors. More precisely, Chios Mastiha-extracted arabinogalactan proteins were tested both *in vitro* and *in vivo*, under the presence of *H. pylori* neutrophil-activating protein, on the innate cellular immune effectors, for the comparison of 5 *H. pylori*-infected patients and 3 healthy controls. Participants received 1g of Chios Mastiha daily for 2 months. Arabinogalactans in Chios Mastiha inhibit neutrophil activation in the presence of *H. pylori* neutrophil-activating protein, playing a vital role in *H. pylori*-linked pathologies in gastric mucosa [13].

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9. Paraschos S., Magiatis P., Mitakou S., Petraki K., Kalliaropoulos A., Maragkoudakis P., Mentis A., Sgouras D., Skaltsounis A.-L. [2007]: In vitro and in vivo activities of Chios mastic gum extracts and constituents against *Helicobacter pylori*. *Antimicrob. Agents Chemother.*, 51 (2): 551–559.

10. Kaliora A.C., Stathopoulou M.G., Triantafillidis J.K., Dedoussis G.V.Z., Andrikopoulos N.K. [2007]: Chios mastic treatment of patients with active Crohn's disease. *World J Gastroenterol.*, 13 (5): 748-753.

11. Kaliora A.C., Stathopoulou M.G., Triantafillidis J.K., Dedoussis G.V.Z., Andrikopoulos N.K. [2007]: Alterations in the function of circulating mononuclear cells derived from patients with Crohn's disease treated with mastic. *World J Gastroenterol.*, 13(45): 6031-6036.

12. Kottakis F., Lamari F., Matragkou C., Zachariadis G., Karamanos N., Choli-Papadopoulou T. [2007]: Arabino-Galactan proteins from *Pistacia lentiscus var. chia*: isolation, characterization and biological function. *Amino Acids*, 34: 413-420.

13. Kottakis F., Kouzi-Koliakou K., Pendas S., Kountouras J., Choli-Papadopoulou T. [2009]: Effects of mastic

Hassan (2009) studied the inhibitory effect of different concentrations of certain plant mucilages and gums (including *P. lentiscus* gum) on specific intestinal disaccharidases. Chios Mastiha possessed the highest inhibitory activity against intestinal invertase, maltase and lactase [14].

Dabos et al (2010) investigated the effect of pure Chios Mastiha on *H. pylori* decrease and eradication, in individuals suffering from *H. pylori* infection. Precisely, 52 patients were randomized and divided into four groups. Group A received 350mg of pure Chios Mastiha three times daily, Group B received 1.05g of pure Chios Mastiha three times daily, Group C received pantoprazole 20mg twice daily plus pure Chios Mastiha 350mg three times daily, and Group D received pantoprazole 20mg twice a day plus amoxicillin 1g twice a day plus clarithromycin 500mg twice a day. The duration of the study equaled 14 days for Groups A, B and C, and 10 days for Group D. Interestingly, eradication of the bacteria was confirmed in 30.8% of patients in Group A and in 38.5% in Group B. Eradication wasn't obtained in any patient in Group C. Additionally, 76.92% of patients in Group D had a negative urea breath test. Chios Mastiha was tolerated well by all participants and no side effects were reported. Thus, Chios Mastiha shows *in vivo* bactericidal activity on *H. pylori* [15].

During the same year, Dabos et al investigated the efficacy of Chios Mastiha in patients with functional dyspepsia. In paricular, 148 patients who fullfilled Rome II criteria for functional dyspepsia were randomly assigned to receive 350mg of Chios Mastiha three times daily or placebo. The study lasted for 3 weeks. Afterwards, the modification in the severity of symptoms of functional dyspepsia was assessed, as well as the subjects' global assessment of efficacy. Interestingly, the symptom score after treatment was significantly lower in Chios Mastiha (14.78±1.78) compared to the placebo group (19.96±1.83). Furthermore, in 40% of patients receiving placebo and in 77% of patients receiving Chios Mastiha there was a remarkable improvement of symptoms. Stomach pain in general, stomach pain when anxious, dull ache in the upper abdomen and heartburn belong to the individual symptoms that demonstrated notable improvement with Chios Mastiha. Therefore, Chios Mastiha significantly improves symptoms in patients with functional dyspepsia compared to the placebo group [16].

In 2011, Gioxari et al conducted a study based upon the hypothesis that Chios Mastiha inhibits intestinal damage in the inflammatory bowel disease, regulating inflammation and oxidative stress in intestinal epithelium. Particularly, 4 doses of P. Lentiscus powder were orally administered in TNBS-colitic rats. As a result, daily administration of 100 mg of Chios Mastiha powder/kg of body weight caused a reduction in all inflammatory cytokines. Hence, Chios Mastiha may potentially exert a therapeutic effect in Crohn's disease, regulating oxidant and/or antioxidant balance and modulating inflammation [17].

In 2012, Kountouras et al claimed that the co-administration of Chios Mastiha, with a *Helicobacter* eradication regimen may cause clinical advantages against *H. pylori*. However, Chios Mastiha possibly was not the main therapy. *H. pylori* neutrophil-activating protein

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gum *Pistacia lentiscus var. chia* on innate cellular immune effectors. *Eur. J. of Gastroenterol. & Hepatol.*, 21(2): 143-149.

14. Hassan H.M.M. [2009]: Inhibitory Activities of Some Mucilages and Gums Against Certain Intestinal Disaccharidases. *Austr. J. Basic & App. Sci.*, 3 (3): 2741-2746.

15. Dabos K.J., Sfika E., Vlatta L.J., Giannikopoulos G. [2010]: The effect of mastic gum in *Helicobacter pylori*: A randomized study. *Phytomedicine*, 17 (3-4): 296-299.

16. Dabos K.J., Sfika E., Vlatta L.J., Frantzi D., Amygdalos G.I., Giannikopoulos G. [2010]: Is Chios mastic gum effective in the treatment of functional dyspepsia? A prospective randomised double-blind placebo controlled trial. *J of Ethnopharmacology*, 127 (2): 205–209.

17. Gioxari A., Kaliora A.C., Papalois A., Agrogiannis G., Triantafillidis J.K., Andrikopoulos N.K. [2011]: Pistacia lentiscus resin regulates intestinal damage and inflammation in trinitrobenzene sulfonic acid-induced colitis. *J. Med. Food*, 14 (11): 1403-1411.

is a promising vaccine candidate against *H.pylori* infection. Finally, the above mentioned protein is also important in the pathogenesis in both gastric and colon oncogenesis [18].

Based on the hypothesis that terpenoids exhibit functional activities via distinguishable pathways, Papalois et al (2012) fractionated Chios Mastiha and applied different fractions or individual oleanolic acid in experimental colitis. Furthermore, the research group investigated the mechanism underlying this effect in human colon epithelial cells. In vivo, histological amelioration of colitis and significant regulation in inflammation occurred with Chios Mastiha powder, even at the mRNA level. Inulin was ineffective. In vitro, Chios Mastiha treatment down-regulated inflammatory IL-8 and NF-κB p65. Because, neither isolated fractions nor individual oleanolic acid were the bioactive component solely, most probably, the entire Chios Mastiha, rather than its individual fractions, reduces inflammation via NF-κB regulation [19].

In 2014, Miyamoto et al studied the chemical composition of Chios Mastiha essential oil and its antibacterial effects against drug-resistant *H. pylori*. More specifically, this study tried to approach which substance of Chios Mastiha was responsible for presenting anti-*H. pylori* activity. Interestingly, 20 constituents were identified by GC–MS. Ten standard components were assayed for anti-*H.pylori* activity, and it was clear that α-terpineol and (E)-methyl isoeugenol showdemonstrated the anti-*H.pylori* action against 4 different *H. pylori* strains that were clinically isolated from patients with gastritis, gastric ulcer and gastric cancer. As a conclusion, these compounds could be useful to overcome the drug-resistant *H. pylori* growth in the gastric environment [20].

A double blind and placebo controlled clinical trial in 128 IBD patients showed, for the first time, that a supplement prepared with Mastiha could be served as an innovative treatment approach as an adjunct to conventional medical therapy. Regulation of faecal lysozyme in active patients points to a prebiotic effect. Additionally, the amelioration of increases in faecal lactoferrin and faecal calprotectin confirms its anti-inflammatory effect in active IBD [21]. Furthermore, in IBD patients in remission, the amelioration in increased plasma amino acids indicates a role of Mastiha in limiting activity of IBD [22].

18. Kountouras J., Zavos C., Deretzi G., Gavalas E., Chatzopoulos D., Katsinelos P., Tsiaousi E., Gagalis S., Polyzos S.A., Venizelos I. [2012]: Potential implications of Helicobacter pylori-related neutrophil-activating protein. *World J. Gastroenterol.*, 18 (5): 489-490.

19. Papalois A., Gioxari A., Kaliora A.C., Lymperopoulou A., Agrogiannis G., Papada E., Andrikopoulos N.K. [2012]: Chios mastic fractions in experimental colitis: implication of the nuclear factor κB pathway in cultured HT29 cells. *J. Med. Food*, 15 (11): 974-983.

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21. Papada E, Gioxari A, Amerik;anou C, Forbes A, Tzavara C, Smyrnioudis I, Kaliora AC, Regulation of Faecal biomarkers in inflammatory bowel disease patients treated with oral mastiha (*Pistacia Lentiscus*) supplement: A double-bind and placebo-controlled randomized trial. Phytother Res. 2018 Nov. 18 doi:10.1002/ptr.6229.

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ANTIOXIDANT & ANTI-INFLAMMATORY ACTIVITY OF CHIOS MASTIHA

Chios Mastiha has been used for ages as an antioxidant factor in fat and oil preservation applications, such as in Egypt in 1970s [23]. In recent years, there has been a constantly increased interest with regards to Chios Mastiha and its antioxidant as well as its anti-inflammatory effects. Interestingly, it has been concluded in various studies that Chios Mastiha inhibits LDL (Low Density Lipoprotein) oxidation *in vitro*. Precisely, this is essential since the resin can be utilized as a natural antioxidant, particularly for fatty substrates in food, cosmetic and pharmaceutical applications. *In vivo* human trials resulted in a remarkable decrease in cholesterol, showing its liver and heart protection characteristics. It is of vital importance to mention that Chios Mastiha's antioxidant activity may have direct impacts to its anti-inflammatory effects. Research has shown the in vivo anti-inflammatory activity of Chios Mastiha in individuals suffering from inflammatory bowel disease, and the inhibition of inflammation in experimental models. Also, Chios Mastiha presents a notable antiatherogenic activity, and thus comprising a potential novel treatment approach for atherosclerosis. It also improves the clinical course in patients with inflammatory Bowel Diseases. The research field of Chios Mastiha in antioxidant and anti-inflammatory applications remains quite promising and challenging enough for even more sophisticated trials in the future.

In 2002, a study group investigated the biological activity of the saliva from different chewing gums, collected from healthy volunteers, on the inhibition of LDL oxidation in vitro. Interestingly, crude Chios Mastiha was indicated as the most effective, followed by commercial Chios Mastiha. Furthermore, in order to obtain the highest possible benefit, chewing time should be from over 15 minutes up to 1 hour [24].

Andrikopoulos et al (2003) studied various resins for their potential protective in vitro activity against copper-induced LDL oxidation. Chios Mastiha has been proved to be the most effective in protecting human LDL from oxidation. The most effective extract of Chios Mastiha was that of methanol/water, compared with other solvent combinations. The total Chios Mastiha essential oil, collofonium-like residue and acidic fractions of the resin possessed also a high protective effect [25].

In 2004, Dedoussis et al explored the molecular mechanisms underlying the antiatherogenic effect of the total polar extract of Chios Mastiha. Apoptosis and necrosis was induced to peripheral blood mononuclear cell (PBMC) exposed to oxLDL, based on the duration of exposure. The extract of Chios Mastiha inhibited both apoptosis and necrosis, restored glutathione levels and downregulated CD36 expression, even at the mRNA level. Interestingly, the triterpenoid fraction of the resin rather than the phenolic one demonstrated remarkable increase in intracellular glutathione. The results comprise strong evidence of the resin's antiatherogenic activity [26].

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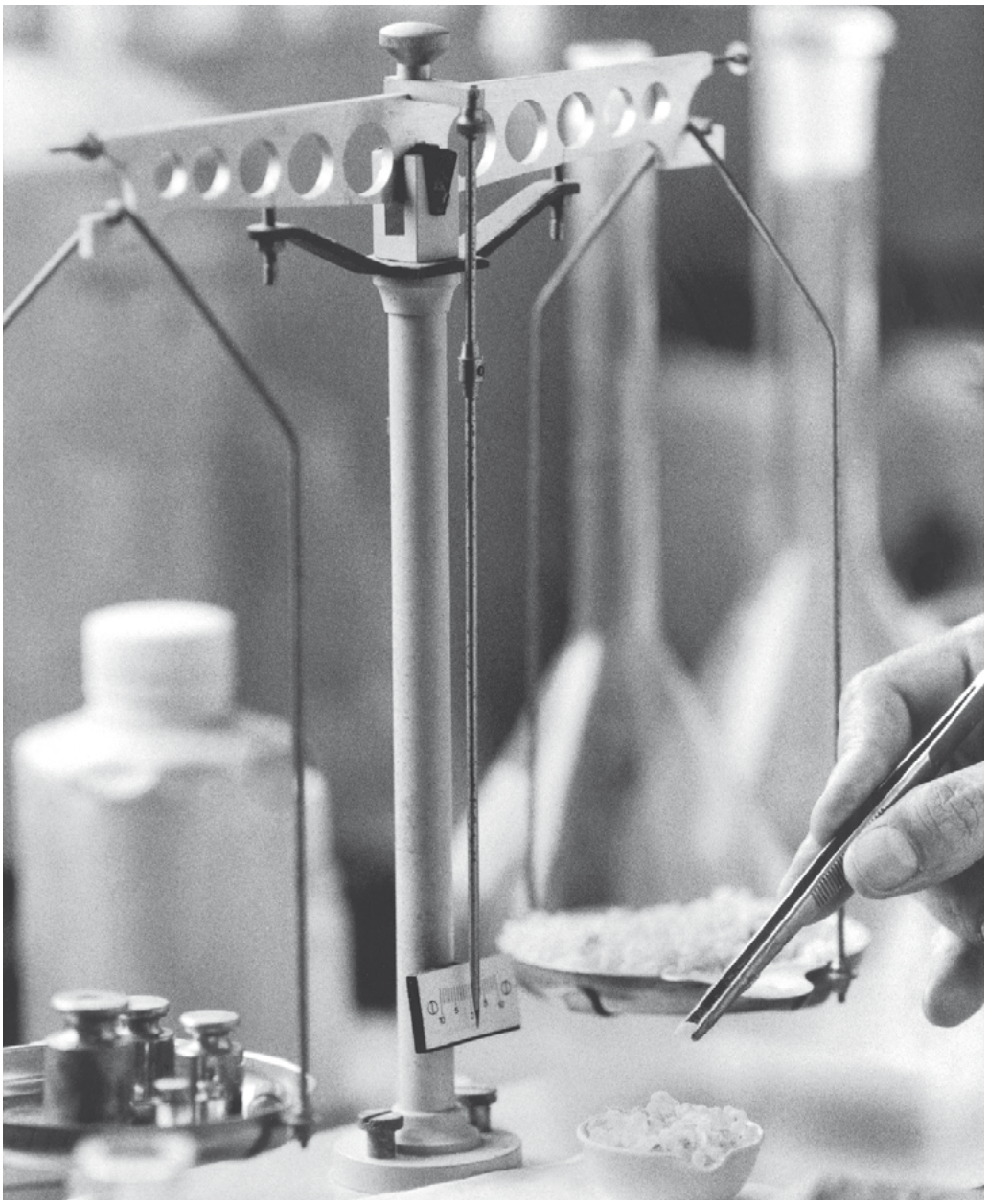
23. Abdel-Ghaffar A.S., El Nawawy A.S., Mohamed M.S. [1957]: The inhibitory effect of mastic gum on bacterial growth. *Alex. Med. J.*, 3: 119-124.

24. Andrikopoulos N.K., Kaliora A.C., Assimopoulou A.N., Papapeorgiou V.P. [2002]: Biological activity of saliva against *in vitro* LDL oxidation after chewing commercial chewing gums. *Ital. J. Food Sci.*, 14 (3): 279-288.

25. Andrikopoulos N.K., Kaliora A.C., Assimopoulou A.N., Papapeorgiou V.P. [2003]: Biological activity of some naturally occurring resins, gums and pigments against *in vitro* LDL oxidation. *Phytother. Res.*, 17: 501–507.

26. Dedoussis G.V.Z., Kaliora A.C., Psarras S., Chiou A., Mylona A., Papadopoulos N.G., Andrikopoulos N.K. [2004]: Antiatherogenic effect of *Pistacia lentiscus* via GSH restoration and downregulation of CD36 mRNA expression. *Atherosclerosis*, 174: 293–303.



In 2005 a research team investigated Chios Mastiha among other natural resins possessing biological properties and the bioactive triterpenes (oleanolic and ursolic acid) for their antioxidant action. Chios Mastiha demonstrated high antioxidant effects in each of the oil substrates examined (lard, corn oil, olive oil and sunflower oil). The best concentration of the resin having the highest effect was substrate-depended. A synergistic effect in sunflower oil and corn oil was observed by the combination of Chios Mastiha with citric acid. *P. lentiscus* showed satisfactory antioxidant action in lard. A significant antioxidant activity was presented by Chios Mastiha and its essential oil, in virgin olive oil. To conclude, Chios Mastiha resin and oil, can be used in pharmaceuticals, cosmetics and functional foods, because of their antioxidant activity in oil substrates [27].

27. Assimopoulou A.N., Zlatanos S.N., Papageorgiou V.P. [2005]: Antioxidant activity of natural resins and bioactive triterpenes in oil substrates. *Food Chemistry*, 92: 721–727.

In 2009, another research group studied whether Chios Mastiha affects the function of activated macrophages. Solid and liquid types of the product were found to inhibit the production of pro-inflammatory compounds, like nitric oxide (NO) and prostaglandin (PG) E2 by lipopolysaccharide (LPS)-activated mouse macrophage-like RAW264.7 cells. Moreover, there was a reduction on the number of viable cells. Chios Mastiha additionally blocked the expression of specific proteins at the protein and at the mRNA levels [28]. Chios Mastiha was found to exhibit potent hydroxyl radical scavenging effects. Conclusively, Chios Mastiha inhibits the production of both NO and PGE2 by activated macrophages mostly via its cytotoxic activity [29].

In 2010, the study of Mahmoudi et al had the objective of investigating Chios Mastiha for its mineral components, anti-inflammatory and antioxidant effects in rats. It was indicated that the resin induced statistically significant inhibition of edema at all doses used, in comparison with the control groups. Inflammation was totally inhibited at 800 mg/kg i.p. and toxicity was absent up to 3 g/kg body weights i.p. in mice. Weak 1,1-diphenyl-2-picryl hydrazyl radical and nitric oxide scavenging activities were observed. However, it showed good Fe2+ chelating ability. Interestingly, the quantity of elements was reduced in the specific order Cu > Fe, Zn > Mn > Ni, Cd. The aforementioned information supports the use of Chios Mastiha resin as an anti-inflammatory and antioxidant agent [30].

In 2011, a research group concluded that Chios Mastiha may help in treating inflammatory diseases, by studying its anti-inflammatory activity in allergic asthma in mice, which is characterized by airway inflammation, eosinophilia, and airway hyperresponsiveness. The product significantly inhibited eosinophilia, while decreasing airway hyperresponsiveness and suppressing the production of inflammatory cytokines, as well as chemokines in bronchoalveolar lavage fluid. Additionally, Chios Mastiha potently inhibited *in vitro* eotaxin-induced eosinophil chemotaxis, without affecting eotaxin receptor, chemokine receptor 3, expression [31].

Triantafyllou et al (2011) explored the potential role of antioxidant activity of Chios Mastiha. Significant scavenging activity of superoxide by Chios Mastiha itself was not shown. The results indicated that Chios Mastiha inhibits PKC, which substantially weakens the production of superoxide and H2O2 by NADPH oxidases, an antioxidant characteristic which may have direct implication to the anti-inflammatory properties of the studied compound [32].

In 2012, Quartu et al evaluated the effect of the administration of Chios Mastiha essential oil on changes of fatty acid profile and endocannabinoid congener concentrations, caused by transient bilateral common carotid artery occlusion in the rat frontal cortex and plasma. It is worth mentioning that ischemia/reperfusion results in inflammation and oxidative stress, damaging membrane highly polyunsaturated fatty acids and subsequently leads to neuronal death. The results showed that acute treatment with Chios Mastiha oil before BCCAO/R elicits changes both in the frontal cortex, where the BCCAO/R-caused deruction of DHA is apparently prevented and COX-2 expression lowers, and in plasma, where PEA and OEA levels and DHA biosynthesis increase. The increase of palmytoylethanolamide

28. Inducible NO synthase (iNOS) and cyclooxygenase (COX)-2.

29. Zhou L., Satoh K., Takahashi K., Watanabe S., Nakamura W., Maki J., Hatano H., Takekawa F., Shimada C., Sakagami H. [2009]: Re-evaluation of anti-inflammatory activity of mastic using activated macrophages. *In vivo*, 23: 583-590.

30. Mahmoudi M., Ebrahimzadeh M.A., Nabavi S.F., Hafezi S., Nabavi S.M., Eslami S. [2010]: Antiinflammatory and antioxidant activities of gum mastic. Eur. Rev. for Med. and Pharm. Sci., 14: 765-769.

31. Qiao J., Li A., Jin X., Wang J. [2011]: Mastic alleviates allergic inflammation in asthmatic model mice by inhibiting recruitment of eosinophils. *Am. J. Respir. Cell Mol. Biol.,* 45: 95–100.

32. Triantafyllou A., Bikineyeva A., Dikalova A., Nazarewicz R., Lerakis S., Dikalov S. [2011]: Anti-inflammatory activity of Chios mastic gum is associated with inhibition of TNF-alpha induced oxidative stress. *Nutrition J.*, 10: 64-72.

and oleoylethanolamide plasma levels may cause DHA biosynthesis via peroxisome proliferator-activated receptor alpha activation, protecting brain tissue from ischemia/reperfusion injury [33].

Gortzi et al (2014) used a total Chios Mastiha extract after the removal of the contained insoluble polymer to improve solubility and *in vivo* activity. Conclusively, the encapsulated fractions of Chios Mastiha, and specifically the acidic one, showed higher antioxidant activity compared to the non-encapsulated fractions [34].

Most recently, in 2018, focusing on the bioavailability of terpenes in human plasma and their effect on oxidative stress biomarkers, an open-label and single arm postprandial trial was carried out. In this acute experiment in healthy adult males, blood samples were collected on time points 0 h (before ingestion) and on subsequent time points after ingestion of Chios Mastiha. Ultra-high-pressure liquid chromatography high-resolution MS (UHPLC-HRMS/MS) was applied for high throughput analysis of plasma. Serum resistance to oxidation and oxidized LDL (oxLDL) levels were measured. In this firstly ever reported study on the bioavailability of Chios Mastiha's compounds in human blood, major terpenes were found bioavailable since 0.5 h after administration, reaching a peak between 2 h and 4 h. Serum resistance to oxidation, expressed as difference of tLAG started to increase from 0.5 h. This increase reached statistical significance at 4 h, peaked at 6 h, and remained statistically significant until 24 h. oxLDL levels, the most reliable marker of oxidative stress expressed as % change from 0 h, was reduced significantly from time point-1 h until time point-6 h. Results demonstrated the terpene bioavailability pattern after oral administration of Chios Mastiha, on the one hand, and on the other the potential of terpenes to mediate antioxidant defense in vivo [35].

Additionally, a total of 24 free amino acids were quantified after mastiha ingestion in plasma. Interestingly, amino acids were modulated in response to mastiha intake, an indicatively potential key role of this natural product in human metabolism [36].

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33. Quartu M., Serra M.P., Boi M., Pillolla G., Melis T., Poddighe L., Del Fiacco M., Falconieri D., Carta G., Murru E., Cordeddu L., Piras A., Collu M., Banni S. [2012]: Effect of acute administration of *Pistacia lentiscus* L. essential oil on rat cerebral cortex following transient bilateral common carotid artery occlusion. *Lipids Health Dis*., 11(8).

34. Gortzi O., Athanasiadis V., Lalas S., Chinou I., Tsaknis J. [2014]: Study of antioxidant and antimicrobial activity of chios mastic gum fractions (neutral, acidic) before and after encapsulation in liposomes. *J. Food Process. Technol.,* 5 (8): 355-359.

35. Papada E, Gioxari A, Brieudes V, Amerikanou C, Halabalaki M, Skaltsounis AL, Smyrnioudis I, Kaliora AC. Bioavailability of Terpenes and Postprandial Effect on Human Antioxidant Potential. An Open-Label Study in Healthy Subjects. Mol Nutr Food Res. 2018; 62(3). doi: 10.1002/mnfr.201700751.

36. Papada E, Torović L, Amerikanou C, Kalogeropoulos N, Smyrnioudis I, Kaliora AC. Modulation of Free Amino Acid Profile in Healthy Humans Administered with Mastiha Terpenes. An Open-Label Trial. Nutrients. 2018 Jun 3;10(6). pii: E715. doi: 10.3390/nu10060715.

ANTI-ATHEROGENIC ACTIVITY OF CHIOS MASTIHA

Interestingly, it has been concluded in various studies that Chios Mastiha inhibits LDL (Low Density Lipoprotein) oxidation *in vitro. In vivo* human trials resulted in remarkable decrease in cholesterol, showing its liver and heart protection characteristics. Chios Mastiha, in relation with the above, presents a notable antiatherogenic activity, expanding the range of studied phytosterols, and thus comprising a possible novel therapy for atherosclerosis.

Loizou et al (2009), investigated the effect of Chios Mastiha neutral extract and tirucallol on the expression of adhesion molecules (VCAM-1 and ICAM-1) and the attachment of monocytes (U937 cells) in TNF-a stimulated Human Aortic Endothelial Cells (HAEC). The impact of the treatment with Chios Mastiha neutral extract and tirucallol in NFkB phosphorylation was studied as well. Interestingly, both substances inhibit VCAM-1 and ICAM-1 expression in TNF-a-stimulated HAEC in a large extend. Furthermore, the binding of U937 cells to TNF-a stimulated HAEC is also significantly inhibited and the phosphorylation of NFkB p65 is weakened. To sum up, by the present research, existing data regarding the cardioprotective effect of Chios Mastiha and the spectrum of known phytosterols with potent antiatheromatic effects are broadened, a novel insight is provided into the mechanisms responsible for the positive effect of Chios Mastiha on endothelial function, and it may assist in designing a potential new therapy for intervention in atherosclerosis [37].

Vallianou et al (2016) evaluated the effect of camphene oil, a constituent of mastiha, on the de novo synthesis of cholesterol and triglycerides from [14C]-acetate in HepG2 cells, along with the statin mevinolin. Camphene inhibited the biosynthesis of cholesterol in a concentration-dependent manner, and a maximal inhibition of 39% was observed at 100 μM while mevinolin nearly abolished cholesterol biosynthesis. Moreover, treatment with camphene reduced TG by 34% and increased apolipoprotein AI expression. In contrast, mevinolin increased TG by 26% and had a modest effect on apolipoprotein AI expression. To evaluate the mode of action of camphene, its effects on the expression of SREBP-1, which affects TG biosynthesis and SREBP-2, which mostly affects sterol synthesis were examined. Camphene increased the nuclear translocation of the mature form of SREBP-1 while mevinolin was found to increase the amount of the mature form of SREBP-2. The effect of camphene is most likely regulated through SREBP-1 by affecting MTP levels in response to a decrease in the intracellular cholesterol. It was proposed that camphene upregulates SREBP-1 expression and MTP inhibition is likely to be a probable mechanism whereby camphene exerts its hypolipidemic effect.[38]

Vallianou et al (2011) assessed the hypolipidemic properties of the Chios Mastiha essential oil, by investigating the hypolipidemic activity of the oil in naïve and in rats susceptible to detergent-caused hyperlipidemia. The consumption of the oil by naïve rats had a dose-dependent decrease in the constitutive synthesis of serum cholesterol and triglycerides. Chios Mastiha oil treatment also possessed a strong hypolipidemic action in hyperlipidemic rat. Analysis of the oil's compounds indicated for the first time that the

37. Loizou S., Paraschos S., Mitakou S., Chrousos G.P., Lekakis I., Moutsatsou P. [2009]: Chios mastic gum extract and isolated phytosterol tirucallol exhibit anti-inflammatory activity in human aortic endothelial cells. *Exp Biol Med.*, 234: 553–561.

38. Vallianou I, Hadzopoulou-Cladaras M. [2016]: Campherne, a plant derived monoterpene exerts its hypolipemic effect by affecting SREBP-1 and MTP expression. PloS One Jan 19;11(1):e0147117. doi: 10.1371/journal.pone.0147117. eCollection 2016.

hypolipidemic effect is linked to camphene. Camphene's administration at a dose of 30 mg/gr of body weight in hyperlipidemic rats led to a 54.5% decrease of total cholesterol, 54% of LDL-cholesterol and 34.5% of triglycerides. The cellular cholesterol content was reduced, after the human hepatic cell line, HepG2, was treated with camphene, to the same level as mevinolin, which is a known HMG-CoA reductase inhibitor. The HMG-CoA reductase action is independent of the hypolipidemic effect of camphene, indicating that the hypocholesterolemic and hypotriglyceridemic effects are connected to a different mechanism of action than the one of statins. Hence, insight is provided into the use of camphene as an alternative lipid reducing agent [39].

Andreadou et al (2016) evaluated the potential anti-ischemic and antiatheromatic activity of Chios Mastiha. Total Chios Mastiha extract without Polymer (TMEWP) and the neutral Chios Mastiha fraction (NMF) were administered orally for 6 weeks to normal fed and to cholesterol fed rabbits. All the animals were randomly divided into 6 groups, anesthetized and subjected to 30min ischemia of the heart, followed by 3h reperfusion: Blood samples were collected at different time points of ischemia and reperfusion, for malondialdehyde (MDA) evaluation as an index of lipid peroxidation, for total and LDL cholesterol determination and for evaluation of oxidized LDL. In the normal fed animals the NMF and the TMEWP reduced significantly the infarct size, while in the hypercholesterolemic rabbits both treatments were ineffective. Atherosclerosis was detected in all animals which were fed cholesterol enriched diet in the form of subintimal accumulation of lipids and foamy macrophages. There was no detection of atherosclerosis in Groups treated with TMEWP and NMF, which both reduced the total cholesterol levels by 47 and 88% respectively, whilst had not effect on LDL oxidation. TMEWP and NMF reduced the MDA concentration in normal fed rabbits, but had no effect on MDA levels in cholesterol fed animals. To conclude, TMEWP and NMPF reduce the infarct size in normal animals and possess significant antiatheromatic and hypolipidemic activities in rabbits fed cholesterol enriched diet [40].

Triantafyllou et al (2007), evaluated the effects of Chios Mastiha on cardiologic and hepatic biochemical indices of human subjects. Precisely, 133 individuals, over the age of 50, were randomly assigned to two groups. More specifically, the first (high-dose group) consumed 5 g of mastic powder per day, whilst the second group (low-dose group) ingested a Chios Mastiha solution per day. The follow up period was 18-month (high-dose group) and a 12-month (low-dose group), and the serum biochemical parameters were determined once per month. The high-dose group demonstrated among others a reduction in serum total cholesterol, LDL and total cholesterol/ HDL ratio. The low-dose group, showed lower glucose levels in males. Ergo, Chios Mastiha powder could have an *in vivo* hepatoprotective and/or cardioprotective role in humans [41].

Kartalis et al (2015) studied the effects of Chios Mastiha on 156 healthy individuals with regards to cholesterol and fasting plasma glucose (FPG) levels, for a total period of eight weeks. The volunteers were divided into 3 groups; the control group ingesting placebo, the total Mastiha group receiving 1 g of crude Chios Mastiha daily (330 mg capsules, tid), the polymer-free Mastiha group taking 1 g of polymer free Chios Mastiha daily (330 mg caps, tid), and the powder Mastiha group receiving 2 g of crude Chios Mastiha per day.

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39. Vallianou I., Peroulis N., Pantazis P., Hadzopoulou-Cladaras M. [2011]: Camphene, a plant-derived monoterpene, reduces plasma cholesterol and triglycerides in hyperlipidemic rats independently of HMG-CoA reductase activity. *PLoS One*., 6 (11): e20516.

40. Andreadou I, Mitakou S, Paraschos S, Efentakis P, Magiatis P, Kaklamanis L, Halabalaki M, Skaltsounis L, Iliodromitis EK. [2016]: Pistacia lentiscus L." reduces the infarct size in normal fed anesthetized rabbits and possess antiatheromatic and hypolipidemic activity in cholesterol fed rabbits. Phytomedicine. 15;23(11):1220-6. doi: 10.1016/j.phymed.2016.06.002.

41. Triantafyllou A., Chaviaras N, Sergentanis T.N., Protopapa E., Tsaknis J. [2007]: Chios mastic gum modulates serum biochemical parameters in a human population. *J Ethnopharmacol.*, 111 (1): 43-49.

As a result, in the total Mastiha group total cholesterol was decreased by 11.5 mg/dl and FPG by 4.5 mg/dl taking into account the age, gender, BMI and baseline properties. Overweight and obese subjects (BMI > 25) showed a stronger effect and the estimated mean decrease of total cholesterol was 13.5 mg/dl ($p < 0.05$) and of FPG 5.1 mg/dl ($p < 0.05$). Interestingly, there were no side effects in the gastrointestinal, liver or renal system. Hence, Chios Mastiha presents an essential reducing activity on total cholesterol and glucose levels of healthy individuals, with exceptional tolerance and no detectable adverse events [42].

Furthermore, Mastiha was investigated in terms of its effect in early markers of oxidation and atheromatosis in an IBD cohort consisting of both Crohn's disease and Ulcerative colitis patients in relapse. Oxidative activity in IBD patients is high and an increased risk for cardiovascular events, such as myocardial infarction and heart failure, has been reported. OxLDL, oxLDL/HDL and oxLDL/LDL decreased significantly in patients administered with Mastiha, indicating the antioxidant/athiatherogenic and cardioprotective effect of this natural supplement [43].

42. Kartalis A., Didagelos M., Georgiadis I., Benetos G., Smyrnioudis N., Marmaras H., Voutas P., Zotika C, Garoufalis S., Andrikopoulos G. [2015]: Effects of Chios mastic gum on cholesterol and glucose levels of healthy volunteers: A prospective, randomized, placebo-controlled, pilot study (Chios-Mastiha). Eur J of Prev Cardiol, Epub ahead of print.

43. Papada E, Forbes A, Amerikanou C, Torović L, Kalogeropoulos N, Tzavara C, Triantafillidis JK, Kaliora AC. Antioxidative Efficacy of a Pistacia Lentiscus Supplement and Its Effect on the Plasma Amino Acid Profile in Inflammatory Bowel Disease: A Randomised, Double-Blind, Placebo-Controlled Trial. Nutrients. 2018 Nov 16;10(11). pii: E1779. doi: 10.3390/nu10111779

ANTIDIABETIC ACTIVITY OF CHIOS MASTIHA

Recent data emphasize on the indisputably positive effects of Chios Mastiha on glucose metabolism. Precisely, researches have shown that Chios Mastiha ameliorates hyperglycemia. Certain components of Chios Mastiha are associated with this effect, such as oleanonic acid and important triterpenoid compounds such masticadienonic acid and isomasticadienonic acid. *In vivo* trials resulted in significant reductions in blood glucose, showing major antidiabetic activity. A large scale human clinical trial draw the conclusion that Chios Mastiha reduces total cholesterol and glucose levels of healthy individuals, with outstanding tolerance.

Petersen et al (2011) conducted a research for more effective and safe antidiabetic substances, and therefore developed a pharmacophore model depending on partial agonists of PPARγ, which is the subtype γ of fatty acid activated transcription factors belonging to the thyroid/retinoid nuclear receptor family. Methyl oleanonate, a component found in *Pistacia lentiscus* var. *chia* oleoresin was selected. Oleanonic acid, the acid of methyl oleanonate, was identified as a PPARγ agonist analysis of Chios Mastiha fractions. It is worth mentioning that other sub-fractions also demonstrated certain biological effects towards PPARγ [44].

Vuorinen et al (2015) also conducted a pharmacophore-based virtual screening to filter a natural product database for possible 11β-hydroxysteroid dehydrogenase 1 inhibitors. The examination was specifically targeted on the triterpenoids of *Pistacia* species. For instance, masticadienonic acid and isomasticadienonic acid, which constitute major triterpenoid substances of Chios Mastiha were found. Both the aforementioned acids selectively inhibited 11β-hydroxysteroid dehydrogenase 1 over 11β-hydroxysteroid dehydrogenase 2 at low levels. Thus, the results indicate that inhibition of 11β-hydroxysteroid dehydrogenase 1 contributes to the antidiabetic activity of the studied commodity [45].

Georgiadis et al (2013), explored the activity of Chios Mastiha on metabolic parameters of diabetic mice. Streptozotocin-induced diabetic 12-week-old male C57bl/6 mice were diverted to three groups, depending on the dose of the product and the duration of administration. After 4 weeks, the consumption of Chios Mastiha led to reduced serum glucose and triglyceride levels in both low and high dose mastic groups. The body weight levels were decreased in the low dose mastic group, in comparison with the control groups. In the end, the low dose group demonstrated outstandingly lower serum glucose, cholesterol, low-density lipoprotein cholesterol and triglyceride levels and ameliorated high-density lipoprotein cholesterol levels. The high dose mastic group had ameliorated serum triglyceride levels. Hepatic steatosis was in part reversed in both low and high dose mastic groups. To summarize, low doses of Chios Mastiha improve glucose and lipid disturbances in diabetic mice, and at the same time relieve hepatic damage [46].

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44. Petersen R.K., Christensen K.B., Assimopoulou A.N., Fretté X., Papageorgiou V.P., Kristiansen K., Kouskoumvekaki I. [2011]: Pharmacophore-driven identification of PPARγ agonists from natural sources. *J. Comput. Aided Mol. Des*., 25 (2): 107-16.

45. Vuorinen A., Seibert J., Papageorgiou V.P., Rollinger J.M., Odermatt A., Schuster D., Assimopoulou A.N. [2015]: Pistacia lentiscus oleoresin: Virtual screening and identification of masticadienonic and isomasticadienonic acids as inhibitors of 11β-hydroxysteroid dehydrogenase 1. *Planta Med*., 81 (6):525-532.

46. Georgiadis I., Karatzas T, Korou L.-M., Agrogiannis G., Vlachos I.S., Pantopoulou A., Tzanetakou I.P., Katsilambros N., Perrea D.N. [2013]: Evaluation of chios mastic gum on lipid and glucose metabolism in diabetic mice. *J Med Food*, 00 (0): 1–7.

Saad Ur Rehman et al (2015) researched the anti-diabetic activity of crude Chios Mastiha in alloxan-treated diabetic rats. Interestingly, Chios Mastiha in the quantity of 100 mg/kg resulted in significant decrease in blood glucose. Therefore, it is indicated that crude Chios Mastiha is effective in diabetes treatment, since it poses a remarkable antihyperglycemic activity by reducing serum glucose level in diabetic rats and by augmenting glucose tolerance in a large degree [47].

Tzani et al (2016), investigated the role of Chios Mastiha in metabolic profile and liver histology in an animal model of NAFLD. Administration of Chios Mastiha at a dose of 20mg/Kg of body weight per day for 4 weeks resulted in lower glucose, triglyceride and interleukin-6 (IL-6) levels and on the same time hepatic steatosis was partially reversed [48].

Triantafyllou et al (2006), studied the effects of Chios Mastiha on metabolic and hepatic biochemical indices of human subjects. More specifically, male subjects receiving daily a Chios Mastiha solution (low-dose group) for 12 months presented significantly lower glucose levels [49].

Kartalis et al (2015) studied the effects of Chios Mastiha on 156 healthy individuals with regards to cholesterol and fasting plasma glucose (FPG) levels, for a total period of eight weeks. The volunteers were divided into 3 groups; the control group ingesting placebo, the total Mastiha group receiving 1 g of crude Chios Mastiha daily (330 mg capsules, tid), the polymer-free Mastiha group taking 1 g of polymer free Chios Mastiha daily (330 mg

47. Saad Ur Rehman M., Hafeez Kamran S., Ahmad M., Akhtar U. [2015]: Anti-diabetic activity of crude Pistacia lentiscus in alloxan-induced diabetes in rats. *Bangladesh J of Pharm*, 10 (3):543-547.

48. Tzani A, Georgiadis, I, Korou LM, Konstantopoulos P, Agrogiannis G, Vlachos I, Doulamis I, Katsilambros N, Perrea D. (2016). Investigation of chios mastic gum effect on metabolic profile in streptozotocin-induced diabetic mice. Atherosclerosis.

49. Triantafyllou A, Chaviaras N, Sergentanis TN, Protopapa E, Tsaknis J: Chios mastic gum modulates biochemical parameters in a human population. *J Ethnopharmacol* 2007; 111: 43-9.

caps, tid), and the powder Mastiha group receiving 2 g of crude Chios Mastiha per day. As a result, in the total Mastiha group total cholesterol was decreased by 11.5 mg/dl and FPG by 4.5 mg/dl taking into account the age, gender, BMI and baseline properties. Overweight and obese subjects (BMI > 25) showed a stronger effect and the estimated mean decrease of total cholesterol was 13.5 mg/dl ($p < 0.05$) and of FPG 5.1 mg/dl ($p < 0.05$). Interestingly, there were no side effects in the gastrointestinal, liver or renal system. Hence, Chios Mastiha presents an essential reducing activity on total cholesterol and glucose levels of healthy individuals, with exceptional tolerance and no detectable adverse events [50].

Fukazawa et al (2017), studied the effect of Chios Mastiha on healthy Japanese men. In particular, daily intake of 5g of Chios Mastiha powder reduced triglyceride levels at 3 months and insulin and HOMA-IR values at 6 months. Chios Mastiha intake combined with exercise reduced triglyceride levels at 3 months and HOMA-IR values at 3 and 6 months [51].

Georgiadis et al (2014) examined the biological mechanisms that could explain traditional usage and recent pharmacological findings. More specifically, the author and the co-authors conducted a review of a relevant scientific literature database regarding studies on Chios Mastiha and on natural products demonstrating peroxisome proliferator-activated receptor (PPAR) agonist activity, and they explored Chios Mastiha as a PPAR modulator. Chios Mastiha chemical composition has been extensively examined and the presence of various substaces, particularly triterpenoids is well established. Precisely, oleanonic acid, oleanolic acid and gallic acid are known to act as PPAR modulators. Conclusively, it is suggested that some compounds of Chios Mastiha on PPARs act synergistically, and more specifically on both PPARs isotypes -α and -γ, which may comprise one of the more essential biological mechanisms via which the commodity exerts its manifold actions [52].

50. Kartalis A., Didagelos M., Georgiadis I., Benetos G., Smyrnioudis N., Marmaras H., Voutas P., Zotika C, Garoufalis S., Andrikopoulos G. [2015]: Effects of Chios mastic gum on cholesterol and glucose levels of healthy volunteers: A prospective, randomized, placebo-controlled, pilot study (Chios-Mastiha). Eur J of Prev Cardiol, Epub ahead of print.

51. Fukazawa T, Smyrnioudis I, Konishi M, Takahashi M, Ki K Hyeon, Nishimaki M, Xiang M, Sakamoto S. (2018). Effects of Chios mastic gum and exercise on physical characteristics, blood lipid markers, insulin resistance, and hepatic function in healthy Japanese men. Food Science and Biotechnology.

52. Georgiadis I., Karatzas T, Korou L.-M., Katsilambros N., Perrea D. [2014]: Beneficial health effects of chios gum mastic and peroxisome proliferator-activated receptors: Indications of common mechanisms. *J Med Food*, 00 (0): 1–10.

HEPATOPROTECTIVE EFFECTS OF CHIOS MASTIHA

Chios Mastiha has been considered to exert hepatoprotective effects since antiquity. Lately, in some studies, there are indications that support this claim.

Katsanou et al (2014) investigated the modulation of CYP1A1 and CYP1A2 enzymes in the liver of male rats, following oral ingestion of Chios Mastiha extract, at the levels of mRNA and CYP1A1 enzyme activity, which was associated with respective enzyme modulation following oral administration of caffeine (control) involving hepatic enzymes in its metabolism. The outcome showed that the administration of Chios Mastiha extract at the recommended dose does not cause remarkable transcriptional modulation of Cyp1α1/2 and subsequent enzyme activity induction of CYP1A1, while effects of the same order of magnitude were observed in the same test system following the administration of caffeine at the mean daily consumed levels [53].

In 2015, Saad Ur Rehman et al used alloxan-treated diabetic rats to explore the anti-diabetic activity of crude Chios Mastiha. It is worth mentioning that, important improvements were observed in liver function in rats that ingested Chios Mastiha, in comparison with the alloxan-treated ones. Conclusively, Chios Mastiha shows hepatoprotective activity and improves the liver micro-environment [54].

Tzani et al (2016), investigated the role of Chios Mastiha in metabolic profile and liver histology in an animal model of NAFLD. Administration of Chios Mastiha at a dose of 20mg/Kg of body weight per day for 4 weeks resulted in lower glucose, triglyceride and interleukin-6 (IL-6) levels and on the same time, hepatic steatosis was partially reversed. [55]

53. Katsanou E.S., Kyriakopoulou K., Emmanouil C., Fokialakis N., Skaltsounis A.L., Machera K. [2014]: Modulation of CYP1A1 and CYP1A2 hepatic enzymes after oral administration of Chios mastic gum to male Wistar rats. *PLoS One*., 9 (6): e100190.

54. Saad Ur Rehman M., Hafeez Kamran S., Ahmad M., Akhtar U. [2015]: Anti-diabetic activity of crude Pistacia lentiscus in alloxan-induced diabetes in rats. *Bangladesh J of Pharm*, 10 (3):543-547.

55. Tzani A, Georgiadis, I, Korou LM, Konstantopoulos P, Agrogiannis G, Vlachos I, Doulamis I, Katsilambros N, Perrea D. (2016). Investigation of chios mastic gum effect on metabolic profile in streptozotocin-induced diabetic mice. Atherosclerosis.

ANTI-HYPERTENSIVE ACTIVITY OF CHIOS MASTIHA

The known protective effects of Chios Mastiha against oxidative and inflammatory pathways, which are implicated to a certain extend in the pathogenesis of hypertension, set the rationale for mastiha's anti- hypertensive activity. In 2018 two studies were publihed, one in animals and one in humans, providing further evidence that mastiha exerts blood pressure lowering effects.

Tzani et al (2018) studied the effects of Chios Mastiha to blood pressure and hypertension induced target organ damage in 2K1C hypertensive rats, which were treated with 40mg/Kg body weight per day of mastiha for 2 weeks. Mastiha's alleviation on the target organ damage is documented by the amelioration of biomechanical properties of the aorta, including the cross sectional area, aortic wall stiffness and thickness reversal of myocardial small vessel hypertrophy. The protective role of mastiha against hypertension was also manifested by maintenance of serum albumin levels. Mastiha also led to a decrease of CRP and IL-6 levels compared to hypertensive animals which did not receive any treatment. The study concluded that mastiha exhibits blood lowering effect via down-regulation of renin excretion associated with attenuation of target organ damage and inflammatory status [56].

Kontogiannis et al (2018) studied the acute effects of Chios Mastiha on peripheral and aortic haemodynamics and associated changes in gene expression of molecules which are involved in pathways related to hypertension. In a randomized, double – blind case controlled crossover design, volunteers were assessed at two consecutive visits with one week apart. Participants were randomly assigned to an oral administration of 2800mg (four tablets of 700mg) of either mastiha or placebo, and haemodynamic parameters were assessed at baseline, 2 and 3 hours after administration. Hypertensive patients presented acute decreases in peripheral and aortic systolic blood pressure and in peripheral pulse pressure after mastiha administration, while no significant changes were observed in normotensive subjects. The gene expression analyses pointed towards down regulation of the proteasome system and the NOX2 pro-oxidant pathway.

Considering that the magnitude of BP drop observed after mastiha administration matches effect sizes observed with first line anti-hypertensive drugs, the study concludes that mastiha may be of clinical utility in hypertension management and in subsequent reduction of cardiovascular risk [57].

56. Aspasia I. Tzani, Ilias P. Doulamis, Panagiotis S. Konstantopoulos, Ermioni D. Pasiou, Afrodite Daskalopoulou, Dimitrios C. Iliopoulos, Ioannis V. Georgiadis, Nikolaos Kavantzas, StavrowK. Kourkoulis, Despina N. Perea [2018]: Chios mastic gum decreases renin levels and ameliorates vascular remodeling in renovascular hypertensive rats. Biomedicine & Pharmacotherapy(2018) 899-906.

57. Christos Kontogiannis, Georgios Georgiopoulos, Kostantinos Loukas, Eleni-Dimitra Papanagnou, Vasiliki K. Pachi, Ioanna Bakogianni, Ageliki Laina, Anastasios Kouzoupis, Kalliopi Karatzi, Ioannis P. Trougakos and kimon Stamatelopoulos [2018]. Chios mastic improves blood pressure haemodynamics in patients with aertial hypertension: impications for regulation of proteostatic pathways. European Journal of Preventing Cardiology 1-4

ANTIMICROBIAL ACTIVITY OF CHIOS MASTIHA

Apart from the anti-*H. pylori* activity, Chios Mastiha shows exceptional antimicrobial, antibacterial and antifungal properties against other microorganisms. In modern times, Abdel-Ghaffar et al (1957) described the biological properties of the resin in Egypt against a bacterium resembling *Bacillus subtillis* [58].

Other past studies have defined the action of Chios Mastiha against numerous food spoilage and foodborne pathogens. Both Gram positive and Gram negative bacteria have been inhibited by the discussed compound in a different extend. The antifungal action of the aqueous extract of Chios Mastiha is also remarkable against dermatophytes. Furthermore, Chios Mastiha essential oil of has been found to possess certain antimicrobial and antifungal activity, and it has been extensively analyzed in order to determine the exact components which are responsible for its antibacterial characteristics.

In 1995, Tassou & Nychas investigated the antimicrobial action of Chios Mastiha oil on *Staphylococcus aureus, Lactobacillus plantarum, Pseudomonas fragi* and *Salmonella enteritidis*. It was indicated that the oil caused inhibition of the growth of the bacteria. More specifically, Gram positive bacteria were mostly inhibited, compared to the percentage of inhibition of the Gram negative microorganisms [59].

In 1999, Ali-Shtayeh and Abu Ghdeib studied Chios Mastiha against dermatophytes (*Microsporum canis, Trichophyton mentagrophytes* and T*richophyton violaceum*), and it was found that it inhibited all three microorganisms by 90-100% [60].

In 2004, a study was conducted to search the activity of sorbic hydroxamic acid (SHA) and Chios Mastiha oil–ethanol (ME) or water-ethanol (WE) emitters on the growth of *Bacillus cereus* in the conditions of high-moisture and high-pH (~8.9) at ambient temperature (25oC). SHA alone or combined with ME emitters inhibited the growth of the bacteria for 14 days in high-pH crumpets [61].

Koukoutsis et al (2004) among others, also studied the effects of various concentrations of potassium sorbate (KS), sorbic hydroxamic acid (SHA), water-ethanol (WE) and Chios Mastiha oil-ethanol (ME) emitters, in plenty of pH values on the growth of spoilage and food safety microorganisms (*Bacillus cereus, Bacillus subtilis, Salmonella enteriditis, Listeria monocytogenes, Saccharomyces cerevisiae and Penicillium notatum*), high-moisture, high-pH products of the bakery industry. ME emitters controlled the growth of most microorganisms, apart from *Listeria monocytogenes*, for 12 to 28 days on agar plates, and inhibition depended on Chios Mastiha volatiles in the package headspace. It is clearly shown that there is a genus specificity to the antimicrobial effect of both WE and ME emitters. Interestingly, the packaging material affected the antimicrobial efficacy of the inhibitor [62].

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58. Abdel-Ghaffar A.S., El Nawawy A.S., Mohamed M.S. [1957]: The inhibitory effect of mastic gum on bacterial growth. *Alex. Med. J.*, 3: 119-124.

59. Tassou C.C., Nychas G.J.E. [1995]: Antimicrobial activity of the essential oil of mastic gum (*Pistacia lentiscus var. chia*) on Gram positive and Gram negative bacteria in broth and in model food system. Int. *Biodeter. & Biodegr.*, 36 (3): 411-420.

60. Ali-Shtayeh M.S., Abu Ghdeib S.I. [1999]: Antifungal activity of plant extracts against dermatophytes. *Mycoses*, 42: 665–672.

61. Koukoutsis J., Smith J.P., Phillips Daifas D., Yayalan V., Cayouette B., Ngadi M., El-Khoury W. [2004]: Control of *Bacillus cereus* in high-ph crumpets. *J. of Food Safety*, 24: 309–324.

62. Koukoutsis J., Smith J.P., Phillips Daifas D., Yayalan V., Cayouette B., Ngadi M., El-Khoury W. [2004]: In vitro

Daifas et al (2004) performed a study on the effect of Chios Mastiha and Chios Mastiha oil, alone and in combination with ethanol, on the growth of *Clostridium botulinum* in media and on neurotoxin production. It was demonstrated that high levels of the resin in ethanol were required to completely inhibit all strains of C. botulinum tested. However, the resin in ethanol showed a significant anti-botulinal activity than ethanol alone. Low levels of the essential oil were needed to inhibit the microorganism. Both experiments showed a strain specific inhibition. It is worth mentioning that the resin in ethanol was more effective when used as a vapor phase inhibitor applied to cotton pads and placed inside inoculated plates than when added directly to the media material [63].

Koutsoudaki et al (2005) investigated the chemical composition of Chios Mastiha oil and gum by using GC-MS. Additionally, the majority of their components was approached, namely α-pinene, β-myrcene, β-pinene, limonene, and β-caryophyllene. An evaluation was carried out, on the antibacterial effects of 12 substances of Chios Mastiha oil and the oil itself, and attempts were conducted for the separation of the oil into different fractions. As a result, verbenone, R-terpineol and linalool were identified as important contributors to the antibacterial activity of the essential oil. Different sensitivity was demonstrated to the aforementioned components for different bacteria (*Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis*). Therefore, the antibacterial activity of the oil depends on the synergy numerous components. Chios Mastiha was analysed as well, however its handling was more difficult [64].

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studies to control the growth of microorganisms of spoilage and safety concern in high- moisture, high-pH bakery products. *J. of Food Safety*, 24: 211-230.

63. Phillips Daifas D., Smith J.P., Blanchfield B., Sanders G., Austin J.W., Koukoutsis J. [2004]: Effects of mastic resin and its essential oil on the growth of proteolytic *Clostridium botulinum*. Int. J. of Food Microb. 94 (3): 313– 322.

64. Koutsoudaki C., Krsek M., Rodger A. [2005]: Chemical composition and antibacterial activity of the essential oil and the gum of *Pistacia lentiscus var. chia. J. Agric. Food Chem.*, 53: 7681-7685.

ANTI-CANCER ACTIVITY OF CHIOS MASTIHA

Numerous studies concern the anti-cancer activity of Chios Mastiha. Precisely, the commodity induces several positive effects on colon or colocteral, lung, oral, pangreas, prostate cancer and leukemia. Recent scientific evidence attributes anti-cancer effects to Chios Mastiha rendering it as a potential future therapeutic agent for the abovementioned -and possibly more- types of the disease which mostly plagues humanity for the past two centuries.

In 2007 a research showed that a 50% ethanol extract of Chios Mastiha contains substances that inhibit proliferation and are responsible for the *in vitro* anoikis type of cell death of HCT116 human colon cancer cells, including events related to caspase-dependent pathways. Additionally, Chios Mastiha might evolve into a chemotherapeutic agent, in order to treat human colon and other forms of cancer [65].

In 2009, the above study was further extended to research the anticancer action of the hexane extract of MG (He-MG) against human colon cancer *in vivo* in mice. As a result, the dose of 200 mg/kg of He-MG per day for 4 consecutive days (followed by 3 days without treatment) administered, and it inhibited tumor growth by 35% in the absence of toxicity after 35 days. Therefore, He-MG demonstrates antitumor activity against human colorectal cancer and the extent of suppression and toxicity, by a particular He-MG quantity, is based on the program of administration [66].

Nasr and Saad (2011) assessed Chios Mastiha in formulation of colon-specific 5-flurouracil delivery system for effective treatment of colorectal cancer. As a result, the concentrations of Chios Mastiha, sodium chloride and hydroxypropyl methyl cellulose in the coating materials of the tablets, remarkably altered drug release. The coating material comprised of 60% Chios Mastiha, 15% sodium chloride and 25% hydroxypropyl methyl cellulose and is considered as a promising formula for achieving colon targeting of 5-flurouracil. Examination in healthy males to assess the *in vivo* release of the coating indicated that tablets stayed intact in the stomach and small intestine. Nevertheless, partial and complete release of the tracer occurred in the colon. The *in vitro* antitumor activity of 5-flurouracil- Chios Mastiha mix showed that the combination was more effective in arresting cell growth compared to the one demonstrated by 5-flurouracil or Chios Mastiha alone. Hence, this novel colonic drug delivery system is potentially useful for 5-flurouracil colon targeting [67].

In 2006, a study group examined whether Chios Mastiha oil suppresses tumor cell growth and angiogenesis, and found that its concentration and time dependently exerted an anti-proliferative and pro-apoptotic activity on K562 human leukemia cells and inhibited the release of vascular endothelial growth factor from K562 and B16 mouse melanoma cells as well. Additionally, the oil generated a concentration-dependent inhibition of endothelial cell proliferation whilst it did not have any effect on cell survival and a significant decrease of microvessel formation both *in vitro* and *in vivo*. In general, the

65. Balan K.V., Prince J., Han Z., Dimas K., Cladaras M., Wyche J.H., Sitaras N.M., Pantazis P. 2007]: Antiproliferative activity and induction of apoptosis in human colon cancer cells treated in vitro with constituents of a product derived from *Pistacia lentiscus L. var. chia. Phytomedicine*, 14 (4):263-272.

66. Dimas K., Hatziantoniou S., Wyche J.H., Pantazis P. [2009]: A mastic gum extract induces suppression of growth of human colorectal tumor xenografts in immunodeficient mice. *In Vivo*, 23 (1): 63-68.

67. Nasr M., Saad I.E. [2011]: Formulation and evaluation of mastic gum as a compression coat for colonic delivery of 5-flurouracil. *Int. J. Drug Del.*, 3: 481-491.

results suggested that Chios Mastiha oil, amid its various effects on malignant cells and endothelial cells, may constitute an expedient natural dietary supplement to prevent cancer [68].

In 2009, a research demonstrated that Chios Mastiha oil decreased vascular endothelial growth factor and chemokine release by Lewis lung carcinoma cells. Moreover, a mechanistic link between Chios Mastiha oil activities and blocking of relevant signaling and transcription pathways was found. A dose-response comparison with perillyl alcohol and alpha-pinene, which comprise two of the oil's ingredients, indicated a higher efficacy of Chios Mastiha oil, aiming to a crucial collective interaction between its components. Ergo, the findings supply new *in vivo* information of the inhibitory activity of the oil on tumor growth and set a rational basis for its application in cancer prevention [69].

Moulos et al studied the mechanisms of action of Chios Mastiha oil at genome-wide gene expression level in Lewis Lung Carcinoma cells, in 2009. As a result, exposure to the oil caused a time-dependent alteration in the expression of 925 genes. Further analysis linked expression profiles with numerous biological processes and functions. Specifically, important mechanistic links underlying the anti-proliferative, pro-apoptotic and anti-inflammatory effects of mastic oil were found. Conclusively, novel evidence was provided on the molecular basis of tumor growth inhibition mediated by Chios Mastiha oil and set the ground for genomics and bioinformatic methodologies' application in the screening of natural substances with potential cancer chemopreventive effects [70].

In 2011, Loutrari et al investigated the anti-metastatic actions of Chios mastiha oil in mouse Lewis lung adenocarcinomas cells. It was shown that treatment of the above cells with the oil within a range of non-toxic concentrations (0.01–0.04% v/v) promoted the multipotent role of Chios Mastiha oil in preventing essential processes relevant to cancer metastasis [71].

In 2008, a study group investigated the *in vitro* effects of cytotoxicity and growth inhibition, and the molecular mechanism underlying modulation of cell cycle and induction of apoptosis in YD9 human oral squamous carcinoma cell line treated with Chios Mastiha. The outcome of the study was that Chios Mastiha can be utilised as a novel therapeutic strategy for human oral squamous cell carcinoma from its strong cell cycle arrest and apoptosis-inducing effects [72].

During the same year, Min et al examined the synergistic apoptotic effect of co-treatment with Chios Mastiha and a CDCA derivative, HS-1200 on human osteosarcoma cells. Apoptotic manifestation was confirmed and the co-treatment interestingly led to prominently apoptosis. Ergo, the combination therapy of Chios Mastiha and HS-1200 could be used as a novel therapeutic strategy for human osteosarcoma [73].

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68. Loutrari H., Magkouta S., Pyriochou A., Koika V., Kolisis F.N., Papapetropoulos A., Roussos C. [2006]: Mastic oil from Pistacia lentiscus var. chia inhibits growth and survival of human K562 leukemia cells and attenuates angiogenesis. *Nutrition and Cancer*, 55 (1): 86–93

69. Magkouta S., Stathopoulos G.T., Psallidas I., Papapetropoulos A., Kolisis F.N., Roussos C., Loutrari H. [2009]: Protective effects of mastic oil from Pistacia lentiscus variation chia against experimental growth of lewis lung carcinoma. *Nutr Cancer.*, 61 (5):640-648.

70. Moulos P., Papadodima O., Chatziioannou A., Loutrari H., Roussos C., Kolisis F.N. [2009]: A transcriptomic computational analysis of mastic oil-treated Lewis lung carcinomas reveals molecular mechanisms targeting tumor cell growth and survival. *BMC Med Genomics*, 15 (2): 68.

71. Loutrari H., Magkouta S., Papapetropoulos A., Roussos C. [2011]: Mastic oil inhibits the metastatic phenotype of mouse lung adenocarcinoma cells. *Cancers* 3: 789-801.

72. Park J.H., Kim G.C., Kwak H.H., Kim I.R., Lee S.E., Chung J., Park H.R., Shin S.H., Choi S.H., Kim C.H., Nam C.O., Park B.S. [2008]: Chios Gum Mastic Induces Cell Cycle Arrest and Apoptosis in YD9 Human Oral Squamous Carcinoma Cells. *Korean J Phys Anthropol.*, 21(1): 55-68.

73. Min J.H., Kim M.J., Kim I.R., Lee S.E., Kwak H.H., Kim G.C., Park H.R., Shin S.H., Kim C.H., Jeong N.Y., Suh H., Park B.S. [2008]: Apoptotic Effect of Co-Treatment with a Natural Product, Chios Gum Mastic, and a Synthetic Chenodeoxycholic Acid Derivative, HS-1200, on Human Osteosarcoma Cells. *Korean J Phys Anthropol.*, 21 (2):

Baek et al (2008) explored the synergistic apoptotic effect of co-treatment with Chios Mastiha and a proteasome inhibitor, lactacystin, on human osteosarcoma cells. The study indicated that the co-treatment of Chios Mastiha together with lactacystin resulted to potentially apoptosis, which each single treatment induced slightly. Additionally, the aforementioned co-treatment potentiated the inhibition of proteasome activity. Thus, the combination of Chios Mastiha and lactacystin could be considered as an innovative therapeutic strategy for human osteosarcoma [74].

Min et al studied the alteration of the cell cycle and induction of apoptosis by Chios Mastiha treatment on human osteosarcoma cells in 2009. The treatment of Chios Mastiha to human osteosarcoma cells led to a dose- and time-dependent reduction in cell viability, a dose-dependent inhibition of cell growth and cell death owing to apoptosis. Further examination of the cells revealed many lines of apoptotic manifestation and G1 arrest in cell cycle progression. To wrap up, it was clearly demonstrated that Chios Mastiha causes G1 cell cycle arrest via the modulation of cell cycle-related proteins, and apoptosis via proteasome, mitochondrial and caspase cascades in human osteosarcoma cells, considering the commodity as a novel therapy for human osteosarcoma.

In 2011, Li et al studied Chios Mastiha as a possible anti-tumor agent for oral squamous cell carcinoma *in vitro*. As a result, Chios Mastiha and Taxol inhibited the proliferation of YD-10B cells in a time- and dose- dependent way. Moreover, Chios Mastiha induced fragmentation of the genomic DNA in 24 hours, and cleavage of procaspase-3. Conclusively, Chios Mastiha can be used as an anti-tumor agent [75].

167-180.

74. Baek C.J., Heo J.Y., Kim G.C., Kwak H.H., Kim I.R., Lee S.E., Kim C.H., Jeong N.Y., Park B.S. [2008]: Apoptotic Effect of Co-Treatment with a Natural Product, Chios Gum Mastic, and a Proteasome Inhibitor, Lactacystin, on Human Osteosarcoma Cells. *Korean J Anat.* 41 (2): 129-138.

75. Li S., Cha I.H., Nam W. [2011]: Chios Mastic Gum Extracts as a Potent Antitumor Agent that Inhibits Growth and Induces Apoptosis of Oral Cancer Cells. *Asian Pac J Cancer Prev.*, 12 (7): 1877-1880.

In 2009, another research team examined the synergistic apoptotic activity of the co-treatment with Chios Mastiha and a CDCA derivative, HS-1200 on G361 human melanoma cells. Despite the absence of apoptosis in the single treatment, the co-treatment induced prominently apoptosis to the cells [76].

A research team in 2010 investigated the anti-proliferative and apoptotic effects of gemcitabine combined with Chios Mastiha, as well as the underlying mechanisms in human pancreatic cancer cell lines. It is of vital importance to mention that Chios Mastiha significantly potentiated the anti-proliferative and apoptotic effects of gemcitabine after a 72 hour treatment. Therefore, the synergy of gemcitabine with Chios Mastiha causes potent apoptosis in pancreatic cancer cells [77].

In 2006, a study group investigated the inhibitory activity of Chios Mastiha on androgen receptor (AR) action, in order to study if the compound might attenuate the function of AR in prostate cancer cells. Androgen-responsive prostate cancer cell line LNCaP was utilised as a model. After a series of analysis was carried out, it was found that the product inhibited the expression of the AR at the transcriptional level, leading to the down-regulation of both AR messenger RNA and protein level. In other words, the function of the AR was inhibited, as indicated *in vitro* [78].

He et al (2007) aimed in studying the effect of Chios Mastiha on the proliferation of androgen-independent prostate cancer PC-3 cells, and subsequently to explore the mechanisms associated with this regulatory system. As a result, the product inhibited PC-3 cell growth and blocked the PC-3 cell cycle in the G1 phase. To put it differently, the proliferation was inhibited and the cell cycle progression in PC-3 cells was blocked by suppressing nuclear factor B activity and signal pathway [79].

Spyridopoulou et al (2017) analysed the volatile dietary phytochemicals which present in Chios Mastiha oil and comparatively investigated their effects on colon carcinoma proliferation, *in vitro* and *in vivo* on tumour growth in mice following oral administration. Chios Mastiha oil inhibited – more effectively than its major constituents- proliferation of colon cancer cells in vitro. When administrated orally, Chios Mastiha oil inhibited the growth of colon carcinoma tumours in mice. A reduced expression of Ki-67 and surviving in tumour tissues accompanied by the observed effects. Thus, Chios Mastiha oil, as a combination of terpenes, exerts growth inhibitory effect against colon carcinoma, suggesting a nutraceutical potential in the fight against colon cancer. Concluding the author's state, the first report shows that orally administrated Chios Mastiha oil induces tumour-suppressing effect against experimental colon cancer [80].

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76. Hur Y.J., Kim Y.K., Kwak H.H., Kim G.C., Lee S.E., Kim I.R., Kim C.H., Park B.S. [2009]: Apoptotic Effect of Co-treatment with Chios Gum Mastic and HS-1200 on G361 Human Melanoma Cell Line. *Korean J Anat*., 42 (2): 83-92.

77. Huang X.Y., Wang H.C., Yuan Z., Li A., He M.L., Ai K.X., Zheng Q., Qin H.L. [2010]: Gemcitabine combined with gum mastic causes potent growth inhibition and apoptosis of pancreatic cancer cells. *Acta Pharmacol Sin*., 31 (6): 741-745.

78. He M.-L., Yuan H.-Q., Jiang A.-L., Gong A.Y., Chen W.-W., Zhang P.-J., Young C.Y.F., Zhang J.-Y. [2006]: Gum mastic inhibits the expression and function of the androgen receptor in prostate cancer cells. Cancer, 106: 2547–2555.

79. He M.-L., Li A., Xu C.-S., Wang H.-L., Zhang M.-J., Gu H., Yang Y.-Q., Tao H.-H. [2007]: Mechanisms of antiprostate cancer by gum mastic: NF-?B signal as target. *Acta Pharmacologica Sinica*, 28 (3): 446-452.

80. Spyridopoulou k. Tiptiri-Kourpeti A., Lampiri E., et all [2017]: Dietary mastic oil extracted from Pistacia lentiscus var. Chia suppresses tumor groth in experimental colon cancer models, Scientific Reports 2017; 7: 3782.

CHIOS MASTIHA AND ORAL HEALTH

In accordance with Herodotus (484–425 BC), Chios Mastiha had been beneficial to oral cavity hygiene. In *De Materia Medica*, Dioscorides (40–90 AD) mentions that Chios Mastiha is useful for cleaning the teeth and for odouring the mouth when chewed. Other relevant citations have been made during the Ottoman period and they last till our times. Undoubtedly, Chios Mastiha is essential for the oral hygiene, due to its antimicrobial action against many oral bacterial species. Countless trials have indicated the strong relationship of Chios Mastiha with antiplaque effects, chronic periodontitis, prevention of caries, peridental disorders, treating of oral malodor and gum disease, and other oral cavity conditions.

Watanabe et al in 1973 performed a double blind randomized control trial to evaluate the clinical and microbiological activity of Chios Mastiha oil dentifrice on chronic periodontitis, by using sonic toothbrush. Particularly, 22 volunteers with chronic periodontitis were randomly divided into 2 groups; the experimental group that used Chios Mastiha oil dentifrice and the sonic toothbrush (11 patients: 6 males, 5 females, average age 63.2 years) and the placebo group that used the sonic toothbrush without Chios Mastiha oil dentifrice (11 patients: 4 males, 7 females, average age 55.5 years). 3 sites per each were subjected. Moreover, at baseline and at 2, 4 and 12 weeks, clinical measurements were carried out by using clinical parameters. What is more, at baseline and at 4 and 12 weeks, subgingival plaque was collected. It is worth mentioning that a quantitative analysis of *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Treponema denticola, Tannerella forsythia, Prevotella intermedia* was performed by using real-time polymerase chain reaction (PCR). Interestingly, there was no remarkable difference among the 2 groups regarding the clinical conditions at baseline. After using sonic toothbrush and dentifrice for 2, 4 and 12 weeks in both groups, notable reduced inflammation was observed. Chios Mastiha group demonstrated an important amelioration on swelling, bleeding, redness of gingiva and plaque accumulation, compared to the control. Solely in Chios Mastiha group a significant suppression of *P. gingivalis* and red complex in the ratio against total bacteria cell counts after 4 week treatment, and P. gingivalis and P. intermedia after 12 week treatment happened. The research group was notably superior to the placebo, with regards to the suppression of *P. gingivalis* at 12 weeks after treatment. Conclusively, the present study suggests that sonic toothbrush and dentifrice may be beneficial for chronic periodontitis, and the useful effect for chronic periodontitis may induce the anti-periodontal-pathogen by Chios Mastiha essential oil [81].

In 1985 and 1986, Topitsoglou et al showed that if Chios Mastiha is systematically used, it can lead to a significant reduction in the amount of formatting or already formed dental plaque. In order this trial to be materialized, 10 volunteers (University students) participated, having low caries rate, and were assigned in 2 groups. More specifically, the first group chewed Chios Mastiha for a duration of 10 days, and the other group chewed a placebo gum. As a result, the amount of microbial plaque was reduced in a large extend in the Chios Mastiha group. Thus, the commodity can be used for preventing caries,

81. Watanabe H., Hagiwara S., Fukuda M., Yuichi I., Tamura N., Suzuki M., Kawasaki D., Fukahori M. [1973]: Double blind randomized control test for the usefulness of mastic compound dentifrice against periodontitis under using sonic toothbrush journal title. *Yakuri To Chiryo*, 38 (10): 915-925.

peridental disorders and oral cavity conditions [82] [83].

Farella et al (2001) focused on examining the effects of prolonged gum chewing on pain, fatigue and pressure tenderness of the masticatory muscles. For this reason, 15 women without temporomandibular disorders were asked to conduct one of the next chewing tasks in 3 distinguished sessions: chewing a very hard gum (Chios Mastiha), chewing a soft gum, and empty-chewing with no bolus. The duration of unilateral chewing of gum or empty chewing was equal to 40 minutes at a constant rate of 80 cycles per minute. Perceived muscle pain and masticatory fatigue in each session, were rated on visual analog scales before, during, and after chewing. Moreover, the evaluation of pressure pain thresholds of masseter and anterior temporalis muscles took place before and right after the chewing tasks, and again after 24 hours. The scores of the visual analog scales for pain and fatigue were remarkably higher solely during the hard gum chewing, and after 10 minutes of recovery they were again reduced, almost to their baseline values. For the pressure pain thresholds no significant alterations were observed, after hard or soft gum chewing. Ergo, the findings imply that the jaw muscles recover rapidly from prolonged chewing activity in subjects without temporomandibular disorders [84].

Another study group researched 6 commercial chewing gums, including Chios Mastiha, to evaluate human response to gum of different rheological properties. Six elderly subjects presenting a broad range of dental conditions and 6 dentate younger adults, participated in the trial. To assess the viscoelastic modifications during chewing a simple bench test for measuring the consistency of chewed gums was used. The results showed relationships between the rheological properties of various gums and the modulation of chewing in people of different age groups. Additionally, there were fluidity and viscosity differences between natural Chios Mastiha and the commercial gums containing synthetic material [85].

In a study conducted in 2003 in Japan, the antiplaque effect of Chios Mastiha chewing gum was examined. More precisely, 20 dental students who were both systemically and periodontally healthy were the subjects of the trial. The effects of Chios Mastiha were assessed from 2 double-blinded, randomized studies. Specifically, in the first test, the inhibitory activity of Chios Mastiha on bacteria in saliva following its use was compared to a placebo gum, after mechanical toothbrushing. Saliva samples were collected at the end of 1, 2, 3, and 4 hours and further handled. In the second examination, the assessment of the effects of Chios Mastiha on de novo plaque formation on tooth surfaces and gingival inflammation took place, over a 7-day period without mechanical oral hygiene, following random use of either Chios Mastiha or placebo gum. The results indicated that the total number of bacterial colonies was remarkably decreased during the 4 hours of chewing Chios Mastiha compared to the placebo gum. Additionally, the Chios Mastiha group showed a notably lowered plaque and gingival index compared to the placebo. To sum up, v chewing gum is a beneficial antiplaque agent in decreasing the bacterial growth in saliva and plaque formation on teeth [86].

In 2006, a research group from Turkey showed that Chios Mastiha possesses significant *in vitro* and *in vivo* antibacterial effect against *S. mutans* and mutans streptococci, and it

82. Topitsoglou-Themeli V., Dangalis P., Lambrou D. [1984]: Chios Mastiha and oral hygiene I: A possible measure for decrease microbial plaque formation. *Hell. Stom. Chron.*, 28: 166-170.

83. Topitsoglou-Themeli V., Kolokotronis A., Dangalis P., Lambrou D. [1985]: Chios Mastiha and oral hygiene II: Differentiation in microbial plaque formation. *Redodontia.*, 2: 56-59.

84. Farella M., Bakke M., Michelotti A., Martina R. [2001]: Effects of prolonged gum chewing on pain and fatigue in human jaw muscles. *Eur. J. Oral Sci.*, 109 (2): 81-85.

85. Anastassiadou V., Siovas S. [2002]: Modulation of chewing rhythms to changes in viscoelasticity of chewing gums in people with different age and dental status. *Stomatologia*, 59 (1): 39-49.

86. Takahashi K., Fukazawa M., Motohira H., Ochiai K., Nishikawa H., Miyata T. [2003]: A pilot study on antiplaque effects of mastic chewing gum in the oral cavity. *J. Periodontol.*, 74 (4): 501-505.

may be a valuable adjunct in the prevention of caries. Specifically, clinical studies were conducted on 25 periodontally healthy individuals. Saliva samples were taken from the subjects immediately before and after Chios Mastiha and placebo gum chewing for 15 minutes. Moreover, saliva samples were collected every 30 minutes as well. The results demonstrate that the bacteria number was notably decreased in saliva samples taken after chewing Chios Mastiha, in comparison with the placebo [87].

In 2006, Sterer investigated the antimicrobial activity of Chios Mastiha, against *Porphyromonas gingivalis*, which is responsible for periodontal diseases and oral malodor production. Chios Mastiha methanolic extract caused inhibition zones, suggesting that it may be utilized as a potential non-toxic agent in treating oral malodor and gum disease [88].

Aksoy et al (2007) performed a study to determine antibacterial activity of chewing Chios Mastiha against the salivary levels of *Streptococcus mutans*, the total number of viable bacteria, and lactobacilli in patients undergoing therapy with fixed orthodontic appliances. In particular, the levels of *S. mutans*, lactobacilli, and total bacteria were estimated before and after chewing Mastiha, and the antibacterial effects of chewing Chios Mastiha against these microorganisms in saliva were compared with a placebo. Additionally, the counts for orthodontically treated subjects were assessed before chewing gum, just after chewing gum, and after 45, 75, 105, and 135 minutes as well. Further analysis was followed, and the total number of viable bacteria was measured. The results demonstrated that just after chewing Chios Mastiha for 15 minutes, a notable reduction of total bacteria and *S. mutans* was observed. The decrease in lactobacilli was not important at later first stage. Nonetheless, after 135 minutes, there was a sifnificant reduction of *S. mutans*, total viable bacteria, and lactobacilli in the buccal cavity after chewing Chios Mastiha compared to the placebo. Chewing Chios Mastiha lowered the total viable bacteria, S. mutans, and lactobacilli in saliva in orthodontically treated patients with fixed appliances. Therefore, Chios Mastiha might be of great value in preventing caries lesions [89].

In 2009, a study team explored the comparison of the effect of Chios Mastiha and a xylitol chewing gum on remineralization of caries-like lesions in situ. The results show a reduction in demineralized surfaces in the subjects. Conclusively, chewing both Chios Mastiha and xylitol chewing gum enhanced the remineralization of caries-like lesions, with similar effects [90].

In 2009, a study group evaluated the biological action of solid and liquid types of Chios Mastiha, by cytotoxicity against fibroblasts, radical scavenging activities and inhibitory effect on cell death of oral polymorphonuclear leukocytes. The product demonstrated selective antibacterial action against *Porphyromonas gingivalis* and *Prevotella melaninogenica*, and no anti-HIV effect. Chios Mastiha caused apoptotic cell death. Interestingly, the cytotoxicity of the commodity against leukemic cells was not diminished during storage. The above results suggest the potential advantageous activity of Chios Mastiha in oral health [91].

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87. Aksoy A., Duran N., Koksal F. [2006]: In vitro and in vivo antimicrobial effects of mastic chewing gum against Streptococcus mutans and mutans streptococci. *Arch. Oral Biol.*, 51 (6): 476-481.

88. Sterer N. [2006]: Antimicrobial effect of mastic gum methanolic extract against *Porphyromonas gingivalis*. *J. Med. Food*, 9 (2): 290–292.

89. Aksoy A., Duran N., Toroglu S., Koksal F. [2007]: Short-term effect of mastic gum on salivary concentrations of cariogenic bacteria in orthodontic patients. *Angle Orthod.*, 77 (1):124-128.

90. Biria M., Malekafzali B., Kamel V. [2009]: Comparison of the effect of xylitol gum- and mastic chewing on the remineralization rate of caries-like lesions. *J. Dentistry*, 6 (1): 6-10.

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Al Mofarji et al (2013) made an assessment in the antibacterial effect of Chios Mastiha against the most common aerobic oral bacteria, focusing on oral streptococci. Particularly, 10 individuals (males and females of 18-60 years old) were randomly assigned to 1.5 grams of Chios Mastiha chewing for 45 minutes. A collection of mouth washes took place before and after chewing for further processing. The results indicated that after chewing Chios Mastiha, the total bacterial count for staphylococci, *Neisseria* and oral streptococci were significantly decreased [92].

In 2014, Biria et al aimed in evaluating the effects of three types of gums on the level of Mutans streptococci, Lactobacilli and pH of the saliva. Therefore, 42 students (20-30 years old) were assigned to three parallel groups. Each group separately used pure Chios Mastiha, xylitol mastic gum and probiotic mastic gum for 3 weeks. The number of microorganisms and pH of the saliva were measured before and after the trial. The level of Mutans streptococci posed a remarkable decrease compared to its baseline value in all groups. The salivary *Lactobacillus* count was augmented in the groups using pure Chios Mastiha and xylitol gum, however it was lower in the probiotic type group, notwithstanding that the modifications were notable solely in the probiotic gum team. Ergo, after using all mastic gums for 3 weeks, a notable drop was observed in the number of Mutans streptococci in the saliva [93].

Lee et al (2014) examined the protective action of Chios Mastiha against H2O2-induced oxidative stress and assessed the autophagic properties caused by Chios Mastiha in human keratinocytes. Interestingly, the pretreatment with Chios Mastiha notably lowered apoptosis in H2O2-exposed HaCaT cells, it enhanced the degradation of caspase-3, caspase-8, and caspase-9; and it caused the formation of the processed PARP. An increase in vesicle formation was caused by Chios Mastiha treatment, in comparison with the control group. There was a decrease in the level of p62 and the conversion of LC3-I to LC3-II underwent an augmentation in Chios Mastiha treated HaCaT cells. Moreover, Chios Mastiha led to increased cleavage of ATG5-ATG12 complex. To wrap up, Chios Mastiha assists in the survival of the cells under stressful conditions, by preventing apoptosis and promoting autophagy. Furthermore, evidence is provided to support the antioxidant activity of Chios Mastiha *in vitro* [94].

Karygianni et al (2014) examined the antimicrobial activity of natural plant and fruit extracts of Mediterranean origin against various microbial species. Five different extracts from *Olea europaea*, Chios Mastiha, and *Inula viscosa* were tested against ten bacteria and one *Candida albicans* strain. Two antimicrobial assays—the minimum inhibitory concentration (MIC) assay and the minimum bactericidal concentration (MBC) assay—were applied. Total Chios Mastiha extract was effective against all of the microorganisms with MIC values ranging from 0.02 mg /mL (*P. gingivalis*) to 10mg/ mL. The mean MBC values were between 0.07 mg/ mL (*P. gingivalis, P. micra*) and 10.00 mg/ mL (*S. mutans, S. sobrinus, E. faecalis, C. albicans*, and *E. coli*). Extract concentrations between 0.07 and 2.50 mg /mL exerted bactericidal effect mainly on strict anaerobic, Gram-negative bacteria (*P. gingivalis, P. intermedia*, and *F. nucleatum*). Overall, Chios Mastiha extract showed considerable antimicrobial activity against oral microorganisms, especially Gram-negative anaerobic bacteria, and could therefore be considered as alternative natural anti-infectious agent which could be used against periodontitis [95].

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The importance of masticatory activity from both an etiopathogenic and therapeutic perspective in orthodontics was investigated by Makaremi et al (2016). The authors conducted a comparative analysis of alveolar expansion using a fixed orthodontic appliance and its development between control subjects and subjects performing intense daily chewing exercises with Chios Mastiha. This gum has two advantages: it has been proved to be very effective and there are no ethical issues with its use, as it is a natural product without any contraindications. They found that the subjects who chewed hard gum, the masticatory forces improved the stability of the molar expansion and straightened the molar axes, indicating the positive relationship between daily chewing of hard gum and maxillary transverse growth. Therefore, the clinical implication was that chewing exercises would allow the subjects to achieve a more balanced occlusal function and dentofacial development [96].

In a recent study published in the *J Periodontol* (Koychev el al, 2017), the antimicrobial properties of Chios Mastiha extract on commensal and pathogenic oral bacteria, as well as its possible cytotoxic effect toward cells of epithelial and mesenchymal origin, were evaluated and compared with the common antimicrobial agents hydrogen peroxide (H_2O_2) and chlorhexidine digluconate (CHX). Oral and periodontal pathogens (*Porphyromonas gingivalis, Streptococcus mutans], Streptococcus oralis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia*, and *Prevotella nigrescens*) were treated with different concentrations of Chios Mastiha extract, 3% H_2O_2, and 0.2% CHX. The cytotoxic effect of Chios Mastiha extract was also tested on four cell lines of epithelial and mesenchymal origin. The results of the study showed that the Chios Mastiha extract led to significantly ($P \leq 0.016$) increased inhibition of the tested periodontal pathogens compared with H_2O_2. Chios Mastiha extract showed beneficial effects on cell viability because viability values of tested cells were significantly ($P \leq 0.016$) lower for cells treated with CHX and H_2O_2 compared with Chios Mastiha extract-treated cells after stimulation for 2, 4, and 6 hours. It was concluded that Chios Mastiha extract can be used, without side effects and the appearance of drug resistance, as an alternative, safe, natural antibacterial agent in the prevention of periodontal disease [97].

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CHIOS MASTIHA IN SKIN CARE

In the 19th century, French pharmacopoeias mentioned Chios Mastiha as a component against skin conditions. Owing to its antimicrobial and adhesive properties Chios Mastiha has found its place in many applications which last until our days, including surgical dressings, wound adhesives, medical strips and skin preparations, such as anti-irritation creams.

In 1986, Mikhail et al investigated among others the increase in adhesive power by a compound tincture of benzoin (CTB) compared to a preparation containing Chios Mastiha (Mastisol, which is an alcohol solution of a mastic compound). It was clearly shown that the latter preparation provided a notably more adhesive strength than that obtained by CTB [98].

Mikhail et al (1989) studied, among others, the same compound (Mastisol) with and without 1/2-inch Steri-Strips (0.5 inch wide), to evaluate certain adhesive methods. With a tension of 2.2 pounds/square inch (1 kg/6.5 cm2), the combination of Mastisol and 0.5 inch Steri-Strips provided the strongest adhesion. The studied application should also be useful, in case other types of surgical dressings must be anchored in place [99].

In 1992, Lesesne studied the postoperative use of wound adhesives, and more specifically of Chios Mastiha and benzoin, USP. The results, indicate that Chios Mastiha not only offers superior adhesive qualities compared with benzoin, USP but it possesses a decreased incidence of postoperative contact dermatitis and subsequent skin discoloration as well. Interestingly, it is important in documenting the reduced appearance of complications and the benefits of Chios Mastiha [100].

Ali-Shtayeh and Abu Ghdeib (1999) examined Chios Mastiha, among an adundance of plant extracts against dermatophytes (*Microsporum canis, Trichophyton mentagrophytes* and *Trichophyton violaceum*). Chios Mastiha inhibited all three dermatophytes by 90-100% [101].

In 2001, a study group investigated the antiphlogistic activity of Chios Mastiha essential oil in skin subjected to epilation, by thermolysis or enzymes in different skin region and peeling. Interestingly, creams containing the above mentioned oil caused a notable decrease in the time period needed to alleviate the irritation caused by epilation or peeling, in comparison with skin regions that received placebo cream treatment and which were deprived of the oil [102].

Yavuzer et al (2005) studied the burst strength of suture closure versus the use of suture and strip together. Conclusively, strip reinforcement with and/or without Chios Mastiha did not provide any supplementary strength in the use of sutures. Furthermore, Chios Mastiha augmented the strip adherence, something essential when strips were the only means to close a wound [103].

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OTHER STUDIES

Through the ages, Chios Mastiha was also well known for its aphrodisiac characteristics. In 2010, for examining this, the trace element zinc was calculated while the quantity released after a certain time of chewing was investigated. Three other commercial chewing gums were examined as well, to compare the results. More specifically, Chios Mastiha or commercial gum was chewed for 1, 2, 3, and 4 hours and the zinc content estimated. The zinc content of Chios Mastiha was compared to that of other natural resins of the same genus (*Pistacia terebinthus* L.) or conifer [*Pinus halepensis* Mill. (*Pinaceae*)], which possess a different secretion mechanism and they are also used as a food additive. Additionally, the zinc content was measured from the resin and plant tissues of the above mentioned plants. Zinc content in the resin was lower compared to that of the plant tissues. Chios Mastiha had a slightly higher zinc concentration than the other samples. Moreover, Chios Mastiha released a small amount of about 0.7 mg kg^{-1} zinc in the mouth and gastrointestinal system after 4 hours chewing duration. The zinc content in commercial gums increased to a high level (up to 2 mg kg^{-1}) in the same treatment, something which was assigned to the zinc uptake from salivary secretions, showing zinc deprivation for the human body [104].

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