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Review Article

Beneficial Clinical Effects of Chios Mastic Gum: A Review

Im JJ[1,2], Jeong HS[2], Chung YA[1,2] and Song IU[3]*

[1]Institute for Bio-Medical Convergence, The Catholic University of Korea, South Korea

[2]Department of Radiology, The Catholic University of Korea, South Korea

[3]Department of Neurology, The Catholic University of Korea, South Korea

***Corresponding author:** In-Uk Song, Department of Neurology, Incheon St. Mary's Hospital, The Catholic University of Korea, #56 Dongsu-ro, Bupyeong-gu, Incheon, 21431, Republic of Korea

Received: September 25, 2017; **Accepted:** October 16, 2017; **Published:** October 27, 2017

Abstract

Chios mastic gum, a resin from the mastic tree, has been traditionally used for therapeutic purposes in Greek medicine, especially for gastrointestinal disorders. Over the past decade, an increasing number of studies have been conducted to investigate the therapeutic effects and potential mechanisms of mastic. This review summarizes the current understanding of chemical composition, beneficial effects, and possible underlying mechanisms of mastic. The major phytochemical constituents of mastic were identified as α-pinene, β-myrcene, β-pinene, β-caryophyllene, and limonene. A wide range of biological properties of mastic has been reported including, but not limited to, the therapeutic effects on gastrointestinal disorders as well as the antibacterial, antioxidant, anti-inflammatory, cardiovascular protective, and anticancer activities. In addition, a small number of studies have suggested the potential neuroprotective effect of mastic. Taken together, although little is known about the mechanisms underlying various beneficial activities of mastic, it is likely that phytochemical constituents of mastic may contribute to its effects through regulating gene expression and cellular activity. Furthermore, this review highlights the need for future research towards clinical application and a potential use of masticas dietary supplements.

Keywords: Chios mastic gum; *Pistacialentiscus*; Beneficial effects; Biological properties

Introduction

Chios mastic gum (hereafter referred to as mastic) is a resin from the mastic tree, *Pistacialentiscus* (L.) var. chia, which is mainly cultivated in the island of Chios, Greece. Mastic has been used for therapeutic purposes, mainly for gastrointestinal disorders, in traditional Greek medicine since antiquity [1]. During the past decade, an increasing number of studies have been conducted on the chemical composition, biological properties, and potential mechanisms of mastic. Notably, it has been reported that mastic has beneficial effects on gastrointestinal problems, bacteria, oxidative stress, inflammation, hyper lipidemia, and cancer. The purpose of this review is to summarize our current understanding of the biological properties and molecular mechanisms of mastic. Furthermore, this review discusses the potential neuroprotective effect of mastic.

Phytochemical Profile of *P. lentiscus*

Several studies have examined the chemical composition of the essential oil and gum of *P. lentiscus*. While both essential oil and gum have been used in investigating chemical profile of mastic, most studies have used essential oil due to its higher solubility for phytochemical experiments. Gas chromatography/mass spectrometry was the most common method for the analysis of the chemical composition of mastic oil and gum. The major constituents of the mastic essential oil and gum were identified as α-pinene, β-myrcene, β -pinene, β -caryophyllene, and limonene, although the relative percentages differ between the essential oil and the gum presumably due to the way they are produced [2-4].

Biological Activities

The biological activities of mastic and information regarding dose/concentration are summarized in Table 1.

Therapeutic effects on gastrointestinal disorders

As mentioned earlier, mastic has been used to treat gastrointestinal problems for thousands of years. The therapeutic uses of mastic initiated the first experimental and clinical studies to investigate the activity of mastic against ulcer and gastritis in the 1980s. In a double-blind clinical trial, 38 patients with duodenal ulcer were randomized to either receive mastic (1g daily, 20 patients) or placebo (1g daily, 18 patients) [5]. After 2 weeks of oral treatment, symptomatic relief was reported in 16 (80%) patients on mastic versus 9 (50%) patients on placebo and endoscopically-proven healing was observed in 14 (70%) patients on mastic versus 4 (22%) patients on placebo, confirming the clinical efficacy of mastic on duodenal ulcer.

The therapeutic effect of mastic on experimentally-induced gastric and duodenal ulcer was also evaluated in rats [6]. Oral administration of mastic (500 mg/kg) resulted in a significant decrease in the intensity of gastric mucosal damages induced by mechanical, chemical, pharmaceutical, and stress methods. In addition, the mastic administration led to a significant reduction of free acidity in mice that had undergone pyloric constriction, and an intense cytoprotective effect was observed in rats that had received 50% ethanol. These results provided evidence for the therapeutic efficacy of mastic and suggested that the anti-ulcer effect of mastic could be due to its mild anti-secretory and local cytoprotective activities.

Mastic's therapeutic effect on gastrointestinal disorders was further confirmed in more recent studies. An animal study showed that mastic oil administration significantly reduced the intestinal damages and bacterial translocation in rats [7]. In another study, pretreatment with mastic led to a decrease of gastric mucosal damages in rats with HCI-ethanol induced gastric lesions [8]. Furthermore, patients who were treated with mastic gum (350 mg three times daily) for their functional dyspepsia over three weeks showed a significant

Citation: Im JJ, Jeong HS, Chung YA and Song IU. Beneficial Clinical Effects of Chios Mastic Gum: A Review. Austin Biol. 2017; 2(1): 1022.

Table 1: Summary of the biological activities of mastic and its dose/concentration.

Activity	First author, Year	Mastic type	Subject	Dose/Concentration
Therapeutic effects on gastrointestinal disorders	Al-Habbal, 1985 [5]	Mastic	Humans	p.o.,1g daily, 2 weeks
	Al-Said, 1986 [6]	Mastic	Rats	p.o., 500 mg/kg
	Heo, 2006 [7]	Mastic oil	Rats	p.o., 1cc/kg, 2 days
	Dellai, 2013 [8]	AQ,CHCl3, EtOAc, MeOH leaf extracts	Rats	i.p.,50, 100, and 200 mg/kg; p.o., 25, 50, and 100 mg/kg
	Dabos, 2010 [9]	Mastic	Humans	p.o., 350 mg,3 times daily, 3 weeks
Antibacterial	Huwez, 1998 [10]	Mastic	*H. pylori* strains	0.06 mg/mL*
	Marone, 2001[11]	Mastic	*H. pylori* strains	50% effect at 125 µg/ml; 90% effect at 500 µg/ml
	Kottakis, 2008 [12]	Mastic-extracted AGPs	*H. pylori* strains	1.4g *
	Kottakis, 2009 [13]	Mastic/mastic-extracted AGPs	*H. pylori* neutrophil-activating proteins, Humans	p.o., 1g daily, 2 months
	Paraschos, 2007 [14]	Total mastic extract without polymer	Mice	p.o., 0.75 mg daily,3 months
	Loughlin, 2003 [15]	Mastic	Mice	p.o., 2 g, twice daily, 7 days
	Bebb, 2003 [16]	Mastic	Humans	p.o., 1 g, 4 times daily, 2 weeks
	Dabos, 2010 [17]	Mastic	Humans	p.o., 350 mg, 3 times daily, 2 weeks; 1.05 g, 3 times daily, 2 weeks
Antioxidant	Andrikopoulos, 2003 [20]	Mastic	LDL oxidation	2.5, 5, 10, 25, and 50 mg
	Assimopoulou, 2005 [21]	Mastic, mastic oil	Oil substrates	0.1 and 0.15% w/w
	Gortzi, 2014 [22]	Total mastic extract without polymer	Encapsulation in liposomes	3 g (Rancimat method); 5 g (DSC)
	Bampouli, 2015 [23]	Mastic leaf extracts	Radical scavenging activity	37.13 ± 2.70 to 43.04 ±1.30 µg/mL(fresh leaves); 37.46 ± 2.30 to 80.75 ±1.93 µg/mL (dried leaves)
Anti-inflammatory	Zhou, 2009 [24]	Mastic	pro-inflammatory substances such NO and (PG)E2	0-100 µg/ml (solid form); 0-0.5% (liquid form)
	Triantafyllou, 2011 [25]	Mastic	Endothelial and smooth muscle cells of rats	0.1-10 µg/ml
	Mahmoudi, 2010 [26]	Mastic	Mice	i.p., 100% effect at 800 mg/kg
	Kaliora, 2007 [27]	Mastic	Humans	p.o., 0.37 g/cap, 6 caps daily, 4 weeks
	Kaliora, 2007 [28]	Mastic	Humans	p.o., 0.37 g/cap, 6 caps daily, 4 weeks
Cardiovascular protective	Loizou, 2009 [30]	Mastic neural extract, tirucallol	Human aortic endothelial cells	25, 50, 100, 200 µg/ml (masticneutral extract); 0.1, 1, 10, 100 µM (tirucallol)
	Dedoussis, 2004 [31]	Mastic	PBMC	270 mg/kg
	Vallianou, 2011 [32]	Mastic	Rats	2.5, 4, 5, and 7.5%
	Triantafyllou, 2007 [33]	Mastic	Humans	5 g, powder, daily, 18 months (high-dose group); one-seventh of the dose taken by the high-dose group, solution, daily, 12 months (low-dose group)
Anticancer	He, 2006 [34]	Mastic	Human prostate cancer cells (LNCaP and PC-3)	6-12 µg/mL
	He, 2007 [35]	Mastic	Human prostate cancer cells (LNCaP and DU-145)	8 µg/mL
	He, 2007 [36]	Mastic	Human prostate cancer cells (PC-3)	40 µg/mL
	Balan, 2005 [38]	Hexane extract of mastic	Human colon cancer cells (HCT116)	25 µg/mL and 50 µg/mL
	Balan, 2007 [39]	Ethanol extract of mastic	Human colon cancer cells (HCT116)	50%
	Dimas, 2009 [40]	Hexane extract of mastic	Mice	i.p., 200 mg/kg, daily, 4 days
	Spyridopoulou, 2017 [41]	Mastic oil	Human colon cancer cells (HT29, Caco-2, murine CT26); mice	67.7% α-pinene and 18.8% myrcene
	Loutrari, 2006 [42]	Mastic oil	Human leukemia cells (K562)	0.01-0.02% vol/vol; 0.01-0.1% vol/vol
	Moulos, 2009 [43]	Mastic oil	Lewis lung carcinoma cells	0.01% vol/vol
	Kim, 2016 [44]	Mastic	Human oral cancer cells (YD-10B)	1, 2, 5, and 10 µg/mL
Neuroprotective	Quartu, 2012 [58]	Mastic oil	Rats	0.14%
	Pacifico, 2014 [59]	Mastic	SK-N-BE(2)-C cells	25, 50, and 100 µg/mL

improvement of symptoms compared to those who received placebo [9].

Antibacterial activity

Since the discovery of *Helicobacter pylori* and its correlation with gastric diseases, numerous studies have been conducted to investigate the anti- *H. pylori* activity of mastic. The first study on the bactericidal effect of mastic against *H. pylori* was an *in vitro* experiment, which showed that even a low concentration of mastic (0.06 mg of crude mastic per milliliter) inhibited the growth of the bacterium and induced structural changes in the bacteria [10]. The results indicated that mastic has anti- *H. pylori* activity and offered a possible explanation for its therapeutic effect on gastrointestinal disorders.

The antibacterial activity of mastic against *H. pylori* was supported by studies that reported the bactericidal effect of mastic at different concentrations on 12 *H. pylori* strains isolated from the patients [11]. Minimum bactericidal concentrations was used to detect the antibacterial activity of mastic with the micro dilution method and it showed that mastic exhibited killing of 50% of the bacteria at a lower concentration (125 μg/ml and 90% at a higher concentration (500 μg/ml). Moreover, transmission electron microscopy analysis revealed the structural changes of *H. pylori* cells including air bubble release and morphological abnormalities.

Further studies attempted to find the constituents of mastic that are responsible for the anti- *H. pylori* activity. In an *in vitro* study, the investigators isolated the Arabino Galactan Proteins (AGPs) from mastic and demonstrated that AGPs obtained from mastic inhibited the growth of *H. pylori* cells [12]. The results from this study suggested that the anti- *H. pylori* activity of mastic could potentially be attributed to the AGPs. Furthermore, the same group investigated the effect of mastic-extracted AGPs both *in vitro* and *in vivo* on the innate cellular immune effectors [13]. The study found that the mastic-extracted AGPs inhibited the neutrophil activation in the presence of *Helicobacter pylori* neutrophil-activating protein. In another study, the anti- *H. pylori* activity of mastic and the active constituents underlying this activity were evaluated [14]. The administration of a total mastic extract without polymer (0.75mg daily) over three months reduced the *H. pylori* colonization approximately 30-fold in mice. Then, a total mastic extract without polymer was separated into an acid and a neutral fraction to identify potential active mastic constituents. The triterpenic acids that were isolated from the acid fraction were found to be the most active constituents against 11 *H. pylori* clinical strains. The study concluded that mastic may be effective in inhibiting *H. pylori* growth and the triterpenic acids may play a major role in this activity.

Despite the accumulating evidence for antibacterial property of mastic, two studies reported that mastic has no bactericidal effect on *H. pylori* [15,16]. The investigations on the activity of mastic in eradicating *H. pylori* infection were carried out in mice [15] and humans [16]. The administration of mastic (2gm twice daily, 7 days) failed to eradicate *H. pylori* infection in mice that were intragastrically inoculated with *H. pylori*. Moreover, the administration of mastic (1gm four times daily, 2 weeks) was not effective in treating patients with *H. pylori* infection. However, in a more recent randomized controlled trial, moderate effect of mastic on *H. pylori* eradication was observed in patients with *H. pylori* infection [17]. Although some studies have provided conflicting results, the majority of studies have found that mastic has bactericidal effect against *H. pylori*.

Antioxidant activity

In the 1970s, two studies from the same group reported that mastic possesses antioxidant activity that is similar to other synthetic phenolic antioxidants used as food preservatives such as Butylated Hydroxy Anisole (BHA) [18,19]. A more recent study examined the protective effect of various resins on the copper-induced Low-Density Lipoprotein (LDL) oxidation and showed that mastic was the most effective in protecting human LDL from oxidation compared to other natural resins [20]. Similarly, several natural resins and triterpenes were investigated for their antioxidant activities using oil substrates for the antioxidant assay [21]. The antioxidant activities of mastic and mastic oil were confirmed with varying degrees of the effects depending on the substrate. In particular, mastic presented considerable antioxidant activity in lard and virgin olive oil, and mastic with citric acid showed a synergistic effect in sunflower oil and corn oil. Notably, two studies investigated the effectiveness of different preparation methods for mastic and revealed that the encapsulated fractions of mastic presented higher antioxidant activity compared with the non-encapsulated ones [22] and fresh leaves showed higher yield and antioxidant potential compared with dried leaves [23].

Anti-inflammatory activity

A growing number of studies have been conducted to elucidate the anti-inflammatory activity of mastic. First, a study showed that mastic has inhibitory effects on the production of pro-inflammatory substances such as Nitric Oxide (NO) and Prostaglandin (PGE2) in Lipopolysaccharide (LPS)-activated macrophages [24]. Moreover, the western blot and real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) analyses revealed that mastic inhibited the expression of inducible NO synthase and Cyclooxygenase-2 (COX-2) at both the protein and mRNA levels. The study suggested that the effect of mastic in inhibiting the production of NO and PGE2 by activated macrophages may be attributed to the cytotoxic action. The anti-inflammatory activity of mastic and its underlying molecular mechanisms were also evaluated in the following studies. In an *in vitro* study, mastic led to the inhibition of the Protein Kinase C (PKC) which attenuates production of superoxide and H_2O_2 by Nicotinamide-Adeninedinucleotide Phosphate (NADPH) oxidases [25]. Furthermore, the anti-inflammatory effect of mastic was also confirmed in a study, which showed that mastic exhibited anti-inflammatory effect on carrageenan-induced edema in mice [26].

The potential role of anti-inflammatory activity of mastic in chronic inflammatory diseases such as Crohn's Disease (CD) has been evaluated [27,28]. Two clinical trials by the same group were conducted to assess the effectiveness of mastic administration on the clinical course and plasma inflammatory mediators [27] and on the cytokine production of circulating mononuclear cells [28] in patients with active CD. In the first study, oral administration of mastic caps (0.37gm per cap, 6 caps daily, 4 weeks) showed that mastic significantly reduced the activity index and the plasma levels of interleukin-6 and C-reactive protein in patients with mildly to moderately active CD. In the second study, the treatment with mastic caps (0.37gm per cap, 6 caps daily, 4 weeks) resulted in a decrease of TNF-α secretion

and an increase of macrophage Migration Inhibitory Factor (MIF) release, indicating inhibition of random migration and chemotaxis of monocytes and macrophages. This study suggested that mastic may play a role in regulating immune function in CD, especially by acting as an immune modulator on peripheral blood mononuclear cells.

Cardiovascular protective activity

Considering mastic's anti-inflammatory and antioxidant activities, several studies have examined the cardiovascular protective effect of mastic. While LDL oxidation and subsequent accumulation of excessive cholesterol in the vascular wall are central to the pathology of cardiovascular diseases, it has been suggested that mastic could potentially protect the cardiovascular system by effectively lowering the levels of cholesterol and inhibiting the LDL oxidation in humans [1,29]. One study in particular investigated mastic's anti-inflammatory effect on human aortic endothelial cells since the early events in the development of other genesis involve the expression of endothelial adhesion molecules [30]. The study found that both mastic neural extract and its constituent, tirucallol, inhibited the Tumor Necrosis Factor-alpha (TNF-α)-induced endothelial activation and expression of adhesion molecules, as well as the phosphorylation of Nuclear Factor kappa B (NF-kB). The results of this study suggest that their anti-inflammatory effect could be attributed, at least in part, to tirucallol and modulation of NF-kB activation, and provides new insight into the cardiovascular protective effect of mastic and potential implications for developing new treatments for atherosclerosis and other cardiovascular diseases. Another study reported that mastic exerted antiatherogenic effects through the restoration of intracellular antioxidant glutathione and down regulation of CD36, a class B scavenger receptor associated with atherosclerotic foam cell formation, expression [31].

Given the central role that hyperlipidemia plays in cardiovascular diseases, the hypolipidemic effect of mastic was evaluated in naïve rats and rats with detergent-induced hyperlipidemia [32]. The mastic administration led to a dose-dependent reduction in the serum cholesterol and triglycerides in both native and experimental rats. Further experiments revealed that camphene, a constituent from mastic, might be responsible for the hypolipidemic activity. In a randomized controlled trial, the effects of mastic on cardiovascular and hepatic functions were evaluated [33]. A total of 133 participants were randomly assigned to either the high-dose group (5gm, powder, daily, 18 months) or the low-dose group (one-seventh of the high-dose group, solution, daily, 12 months), and various biochemical indices were measured monthly. The patients in the high-dose group exhibited a reduction in serum total cholesterol, LDL, total cholesterol/high-density lipoprotein ratio, lipoprotein, apolipoprotein A-1, apolipoprotein B, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and γ-glutamyltransferase levels, and the patients in the low-dose group exhibited decreased glucose levels in male patients.

Anticancer activity

A number of studies have been conducted to investigate the anticancer activity of mastic against various types of cancer including prostate cancer, colon cancer, oral cancer, lung carcinoma, and leukemia. One research group performed several studies to examine mastic's anticancer activity against prostate cancer cells and its underlying mechanisms [34-36]. First, while it has been reported that androgens may be involved in the development and progression of prostate cancer, the researchers found that mastic had an inhibitory effect on the expression of the androgen receptors *in vitro* [34]. In the following studies, the researchers also found that mastic exhibited anti-cancer effects *via* enhancing the expression of maspin, a tumor suppressor protein [35], and attenuating the proliferation of androgen-independent prostate cancer PC-3 cells by inhibiting NF-kB activity [36]. These findings provide a deeper understanding on the mechanism of carcinogenesis as inflammation is associated with the development of cancer and the NF-kB pathway is thought to be involved in the process that leads inflammation to carcinogenesis [37].

On the anticancer activity of mastic against colon cancer, two studies by the same group reported that a hexane extract and a 50% ethanol extract of mastic exhibited apoptosis of HCT116 human colon cancer cells *in vitro*, possibly through a caspase-related mechanism [38,39]. This group further explored the anticancer activity of the hexane extract of mastic in a human colon cancer/immunodeficient mouse model and found a decrease of tumor growth by approximately 35% in mice treated with the intraperitoneal administration of mastic (200 mg/kg, daily, 4 days) after 35 days [40]. Furthermore, mastic's anticancer activity against colon cancer was confirmed in a recent *in vitro* and *in vivo* study, which showed that mastic oil induced tumor-suppressing effects on the colon cancer cell lines as well as in mice [41].

A small number of studies have also been performed on the antitumor activity of mastic against other types of cancer besides prostate and colon cancer. One study reported that mastic oil inhibited the growth and survival of K562 human leukemia cells and attenuated angiogenesis [42]. Another study showed that treatment of Lewis lung carcinomas with mastic oil caused a time-dependent alteration in the expression of 925 genes of which many are associated with biological processes and functions of anticancer effects [43]. Lastly, a recent study reported that mastic treatment led to a dose-dependent growth inhibition of YD-10B human oral cancer cells and induced a morphological change in the cells [44]. The studies on the anticancer activity of mastic pointed to the conclusion that mastic exerts anticancer effect through inhibition of cancer cell proliferation, angiogenesis, and inflammatory response.

Other activities

In addition to the mastic's beneficial effects reviewed above, studies have been conducted on other properties of mastic such as antimicrobial [45-49] and antidiabetic [50-53] activities. Moreover, the effectiveness of mastic use in surgical strips and tapes has also been the subject of investigation [54-56]. On the other hand, the toxicity of mastic has been studied in animals [57].

Potential Neuoprotective Effect

While there are an increasing number of studies on various beneficial effects of mastic, the potential neuroprotective effects are still not clear due to the lack of research in this area. Since the reports on the neuroprotective role of Docosahexaenoic Acid (DHA), the effect of mastic oil on DHA has been investigated using a rat ischemia-reperfusion model [58]. In the frontal cortex of rats, pretreatment with mastic oil before the transient Bilateral Common Carotid Artery

Occlusion (BCCAO) prevented the decrease in DHA and COX-2 levels. In plasma, the administration of mastic oil after the BCCAO increased both the ratio of DHA-to-its precursor, eicosapentaenoic acid, and levels of palmitoylethanolamide and oleoylethanolamide, which may induce DHA biosynthesis. The results from the study suggested that mastic may exert brain protective effects against ischemia-reperfusion injury.

As oxidative stress and inflammation are implicated in the pathogenesis of neurodegenerative disorders, the studies on the antioxidant and anti-inflammatory activities of mastic mentioned earlier are also relevant to this topic. While oxidative stress is considered one of the earliest events of Alzheimer's disease and seems to play an important role in amyloid-beta production, neuroinflammation, and neuronal apoptosis, one study investigated the phenol composition of an alcoholic mastic extract to identify metabolites that have antioxidant activity [59]. The analysis revealed that mastic exhibited cytoprotective effects on H_2O_2 and Aβ (25-35) oxidative injury in SK-B-NE(2)-C human neuronal cell lines. Moreover, it has been reported that there is a high prevalence of *H. pylori* in patients with Parkinson's disease [60]. Given the reported anti- *H. pylori* effects of mastic, it may be assumed that mastic will exert therapeutic effects against this common neurodegenerative disorder. However, this assumption is based on indirect evidences and warrants future studies.

Conclusion

In this review, we summarized the current understanding of phytochemical constituents, biological properties, and possible underlying mechanisms of mastic. Studies have revealed therapeutic effects of mastic on gastrointestinal disorders, *H. pylori*, oxidative stress, inflammation, cardiovascular disease, and cancer. A small number of studies have also suggested the potential neuroprotective effect of mastic. Taken together, although little is known about the molecular basis involved in various beneficial activities of mastic, it is likely that mastic directly or indirectly modulates gene expression involved in the inhibition of cell proliferation, inflammatory response, and oxidative stress. On this regard, future studies are needed to further understand molecular mechanisms underlying mastic's activities and specific constituents that are involved, as well as to bridge the gap between preclinical and clinical studies. Given the high demand for the development of natural health-promoting products, potential use of mastic for therapeutic use or dietary supplements may be of importance. In particular, it might be beneficial to develop mastic-containing food products with easy administration such as chewing gum or drinks.

Acknowledgment

This research was supported by the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (MSIT, Korea) (2015M3C7A1064832).

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