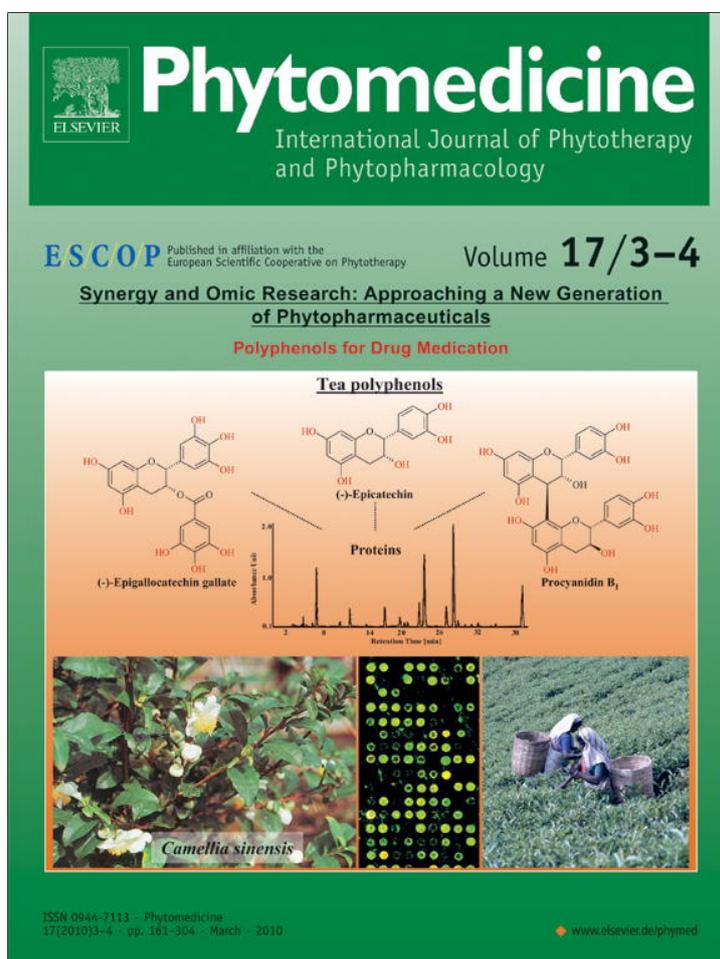


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Short Communication

The effect of mastic gum on *Helicobacter pylori*: A randomized pilot study

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ABSTRACT

Our aim was to study the effect of pure mastic gum on *Helicobacter pylori* (*H. pylori*) eradication in patients suffering from an *H. pylori* infection

Fifty two patients were randomized to receive either 350 mg three times a day (tid) of pure mastic gum for 14 days (Group A), or 1,05 g tid of pure mastic gum (Group B) for 14 days, or pantoprazole 20 mg twice a day (bd) plus pure mastic gum 350 mg tid for 14 days (Group C) or pantoprazole 20 mg bd plus amoxicillin 1 g bd plus clarithromycin 500 mg bd for 10 days (Group D). All patients harboured *H. pylori* before entering the study and that was confirmed by a ¹³C urea breath test (UBT). *H. pylori* eradication was tested by a UBT 5 weeks after completion of the eradication regime.

Eradication of *H. pylori* was confirmed in 4/13 patients in Group A and in 5/13 in Group B. No patient in Group C achieved eradication whereas 10/13 patients in Group D had a negative UBT. There were no statistically significant differences in mean UBT values in Groups A, B, C although there was a trend in Group A ($p=0.08$) and in Group B ($p=0.064$). The difference was significant in Group D ($p=0.01$). All patients tolerated mastic gum well and no serious adverse events were reported. Mastic gum has bactericidal activity on *H. pylori* *in vivo*.

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Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral bacterium that colonises the stomach. Its prevalence in Europe is in the range of 10–25% and has been falling during the last decades while in the developing world it is estimated that its prevalence is much higher (Magalhaes-Queiroz and Lizza 2006). Infection with *H. pylori* is etiologically linked to gastritis, peptic ulcer disease, primary B cell gastric lymphoma and adenocarcinoma of the stomach (Lai and Sung 2007; Eslick 2006). *H. pylori* can be eradicated but this is difficult to achieve and at least two antibiotics and an acid suppressant are required to achieve eradication (Malfetrheiner et al. 2007). Side effects for these regimes are common and a major concern is the development of antimicrobial resistance. Development and testing of new safe alternatives to those regimes is therefore warranted.

Mastic gum is a natural resin that is excreted from the trunk and branches of the mastic bush (*Pistacia Lentiscus* var. *Chia*). This excretion is produced by incising the bark with a sharp instrument. Mastic gum appears in the incisions in the form of tears and exudes in droplets onto the soil. While it is flowing, it is a gummy, clear liquid; it solidifies in irregular shapes after 15–20 days.

Collection is completed in September. Then it is cleaned first by hand and then with mechanized means. Finally mastic gum is

sorted, classified and graded according to the color and size of the granule.

The clean mastic gum granules were milled to fine powder (particle size < 200 μm) by using a Hosokawa Alpine Fine Impact Mill 100 UP2 (Hosokawa Alpine, Augsburg, Germany). The encapsulation of powder was performed using the Profill Capsule Filling System (Torpac Inc, Mumbai, India). Capsule shells (Capsulegel, V caps, size 0) were made of Hypromellose (Hydroxypropyl methylcellulose) and each contained 0.35 (± 0,002) g of mastic powder.

There have been references to mastic gum as a medicinal product since ancient times. It has successfully been used in gastrointestinal upsets (Kaliora et al. 2007).

Previous studies have shown some effect of mastic gum on the healing of peptic ulcers in humans (Al-Habbal et al. 1984; Al Said et al. 1986). Those studies were conducted before the discovery of *H. pylori*. A recent case study has shown no effect of mastic gum on *H. pylori* (Bebb et al. 2003).

The aim of our randomised controlled trial was to assess the efficacy of mastic gum monotherapy or in combination with a proton pump inhibitor on *H. pylori* eradication and to compare this efficacy with the standard treatment regime.

Patients and methods

This prospective randomized controlled trial study was conducted at the Gastroenterology Department of Chios General

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Hospital Skylitsion. The study was approved by the Local Ethics Committee and the Greek Medicines Agency.

All eligible patients had an upper gastrointestinal endoscopy and were found to harbour *H. pylori* by a rapid urease test (CLO test, Kimberky Clark, Draper, Utah, USA). They were then asked to participate in the study and gave their written informed consent. Patients were excluded if they had a gastric or duodenal ulcer, were pregnant women or had used in the previous 4 weeks, non steroidal anti-inflammatory drugs, anticoagulants, steroids, proton pump inhibitors or antibiotics. Patients who chewed mastic gum more than once a week were also excluded from the study.

Patients had confirmation of their *H. pylori* infection by a ^{13}C urea breath test (UBT) (INFAI, York, UK). They were then randomized to receive either a low dose mastic gum monotherapy 350 mg three times a day (tid) for 14 days, a high dose mastic gum monotherapy 1 g tid for 14 days, a dual regime of mastic gum 350 mg tid and pantoprazole 20 mg bd for 14 days, or a standard triple therapy which consisted of pantoprazole 20 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd for 10 days.

They were asked to keep a log of adverse events. One week into the study patients received a telephone call, in which their compliance was assessed and an enquiry on possible adverse events was made. At the end of the study a physical examination was performed as well as routine laboratory tests.

Five weeks after the end of treatment, eradication was tested with a second UBT.

Pure mastic gum was dispensed in capsule form. It contained no additives or flavourings that could have an effect on its activity.

The randomization was generated using Proc random (SAS version 6.9). The randomization code was kept at the Central Pharmacy of Chios General Hospital Skylitsion. The technician who performed the UBTs and the operator who analysed the UBTs were blinded as to which treatment each patient had received.

Data record and statistical analysis

Data were recorded prospectively in case report forms for all participating patients. All analysis was conducted by intention to treat. Results are shown as mean and SEM.

Comparisons between UBT values before and after the intervention were made using the paired t-test. A *p* value of < 0.05 was taken as significant (two-tail test of significance).

Results and discussion

We enrolled fifty two patients from the Endoscopy unit: 13 received low mastic gum monotherapy 350 mg tid for 14 days (Group A), 13 received high mastic gum monotherapy 1 g tid for 14 days (Group B), 13 received mastic gum 350 mg tid and pantoprazole 20 mg bd for 14 days (Group C) and 13 patients received triple therapy with pantoprazole 20 mg bd, amoxicillin 1 g bd and clarithromycin 500 mg bd for 10 days (Group D).

There were no statistically significant differences between groups with regards to age, sex, previous use of antibiotics or proton pump inhibitors.

One patient from Group A completed the study but did not return for his follow up UBT 5 weeks later. Two patients from Group C completed the study but did not return for their UBT 5 weeks later. One patient in Group D stopped because of side effects (diarrhoea and abdominal cramps).

Table 1 shows an overview of the results. Four patients in group A achieved eradication (30.8%), whereas five in Group B (38.5%) none in Group C and ten patients in Group D (76.92%) achieved eradication.

Table 1

Patients in Group A received low dose mastic gum monotherapy for 14 days. Group B patients received high dose mastic gum monotherapy for 14 days. Group C patients received mastic gum and pantoprazole for 14 days. Group D received triple therapy with pantoprazole, amoxicillin and clarithromycin for 10 days. Results are shown as mean \pm SEM

	Eradication	UBT pre	UBT post	p
Group A	4/13 (30.8%)	28.86 \pm 4.4	18.76 \pm 3.1	0.08
Group B	5/13(38.5%)	27.11 \pm 5.2	17.68 \pm 4.8	0.064
Group C	0/13	25.56 \pm 3.8	23.67 \pm 4.7	NS
Group D	10/13 (76.92%)	26.73 \pm 3.9	7.85 \pm 2.8	0.01

Abbreviations: UBT=Urea breath test values.

UBT was performed a mean of 8 days (4–14 days) before starting treatment. It was repeated a mean of 39 days (33–61 days) after completion of the study medication. Fig. 1 shows mean UBT values before and after treatment. There was a trend towards significance in Group A (28.86 \pm 4.4 vs 18.76 \pm 3.1) (*p*=0.08), and in Group B (27.11 \pm 5.2 vs 17.68 \pm 4.8) (*p*=0.064). Group C showed no difference (25.56 \pm 3.8 vs 23.67 \pm 4.7) (*p*=NS) There was a statistically significant difference in UBT values in Group D (26.73 \pm 3.9 vs 7.85 \pm 2.8) (*p*<0.01). In nine patients in Group A and ten patients in Group B the UBT value post treatment decreased compared with the UBT value before treatment.

Patients who received mastic gum tolerated it well. One patient in Group A complained of diarrhoea and another in Group B complained of nausea. Both completed the therapy as per protocol. Three patients in Group D complained of abdominal cramping and diarrhoea, one stopped the treatment on day 4.

This study was designed to evaluate the effect of Mastic gum on *H. pylori* *in vivo*. Our results showed that mastic gum has some effect on *H. pylori* *in vivo*. Nine patients in the monotherapy groups achieved eradication while in ten more patients the UBT value decreased compared to the pre-treatment reading. UBT values have been shown to provide rather accurate estimation of the *in vivo* *H. pylori* load (Perri et al. 1998).

We have also shown that the combination of mastic gum and pantoprazole was ineffective in eradicating *H. pylori* but it had no effect on bacterial load either. Our control group with standard triple therapy achieved an acceptable eradication rate.

The constituents which might contribute to the therapeutic effects of mastic gum belong to the class of mono- and sesquiterpenoids (essential oils) (Barra et al. 2007) and triterpenoids (e.g. masticadienonic acid) (Assimopoulou and Papageorgiou 2005). Previous *in vitro* studies have shown that crude mastic gum possesses antibacterial properties against *H. pylori* (Huwez et al. 1998; Marone et al. 2001). A recent study has shown that the acid fraction of mastic gum which contains triterpenic acids and constitutes about 50% of its total weight has bactericidal activity against *H. pylori* (Paraschos et al. 2007). In particular, moronic acid seems to be a powerful antibiotic not only against *H. pylori* but also other bacteria (Hostettmann-Kaldas and Nakanishi 1979).

The activity of mastic gum against *H. pylori* *in vivo* was the subject of studies with conflicting results. Early studies showed bactericidal activity on *H. pylori* *in vitro* and it was hypothesized that mastic gum killed *H. pylori* and thus helped ulcer healing (Huwez et al. 1998; Marone et al. 2001). Unfortunately, two recent *in vivo* studies, one in mice and the other in humans showed no eradication of *H. pylori* and only a modest antibacterial activity (Bebb et al. 2003; Loughlin et al. 2003).

Mastic gum is a herbal remedy and all studies that used mastic gum on patients showed minimal side effects (Al-Habbal et al. 1984; Al Said et al. 1986; Bebb et al. 2003). Also a recent study on animals showed that long term use of mastic gum was not

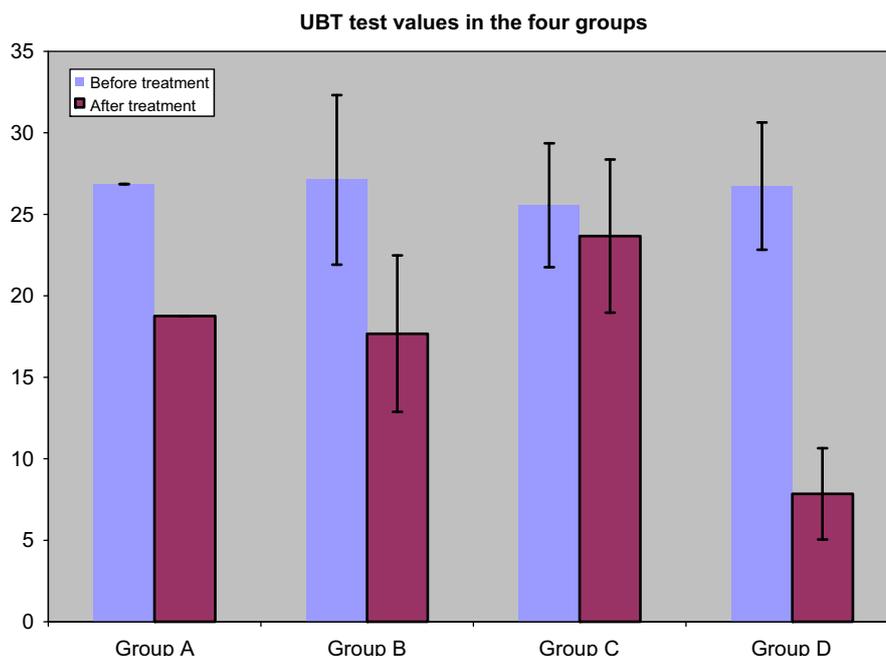


Fig. 1. Urea breath test (UBT) was reformulated a mean of 8 days (4–14 days) before starting treatment. It was repeated a mean of 39 days (33–61 days) after completion of the study medication. Mean values of UBT before and after treatment are shown. There was a trend towards significance in Group A (28.86 ± 4.4 vs 18.76 ± 3.1) ($p=0.08$), and in Group B (27.11 ± 5.2 vs 17.68 ± 4.8) ($p=0.064$). Group C showed no difference (25.56 ± 3.8 vs 23.67 ± 4.7) ($p=NS$). There was a statistically significant difference in UBT values in Group D (26.73 ± 3.9 vs 7.85 ± 2.8) ($p < 0.01$).

associated with serious side effects (Kang et al. 2007). As a considerable fraction of patients harbouring the bacterium are unable to tolerate triple therapy due to side effects mastic gum might provide a reasonable alternative in the future.

The fact that the combination of mastic gum and pantoprazole showed no effect on *H. pylori* is somewhat surprising. Most active substances of mastic gum belong to its acidic fraction. They possibly require an acidic environment in the stomach to successfully kill *H. pylori*. Proton pump inhibitors block the hydrogen – potassium ATP enzyme system on the gastric parietal cells. In that way, they increase the intragastric pH. Buffering the acidity of the stomach by the proton pump inhibitors could result in a hostile environment for mastic gum. This hypothesis needs to be tested in further studies.

We have used two doses of mastic gum in our study the main reason being that a low dose mastic gum monotherapy has shown some activity in a previous study (Al-Habbal et al. 1984) while a high dose monotherapy has been shown to be ineffective in another study (Bebb et al. 2003).

Our study has limitations, the main one being its small size. We also did not use two different methods of confirming *H. pylori* status after treatment as a second endoscopy was deemed inappropriate.

In conclusion, this proof of principle study showed that mastic gum possesses antibacterial activity against *H. pylori in vivo* and is able to eradicate it from patients. Although even the high dose monotherapy did not achieve acceptable eradication rates it could be used as an alternative regime in patients unwilling to undergo eradication with the triple therapy regime.

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Ekaterini Sfika was an employee of the sponsor during the study period

Lisa Jo Vlatta and Georgios Giannikopoulos have nothing to declare

The study is registered with Controlled Trials and its registration number is ISRCTN01756929 The URL of the trial register is www.controlled-trials.com

References

- 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, 541–544.
- Al Said, M., Ageel, A.M., Parmar, M.S., Tariq, M., 1986. Evaluation of mastic a crude drug obtained from *Pistacia lentiscus* for gastric and duodenal anti-ulcer activity. *J. Ethnopharmacol.* 15, 271–278.
- Assimopoulou, A.N., Papageorgiou, V.P., 2005. GC-MS analysis of penta- and tetracyclic-triterpenes from resin of *Pistacia* species. Part II. *Pistacia terebinthus* var. Chia. *Biomed. Chromatogr.* 19 (8), 586–605.
- Barra, A., Coroneo, V., Dessi, S., Cabros, P., Angioni, A., 2007. Characterization of the volatile constituents in the essential oil of *Pistacia lentiscus* L. from different origins and its antifungal and antioxidant activity. *J. Agric. Food Chem.* 55 (17), 7093–7098.
- Bebb, J.R., Bailey-Flitter, N., Ala'Aldeen, D., Atherton, J.C., 2003. Mastic gum has no effect on *Helicobacter pylori* load in vivo. *J. Antimicrob. Chemother.* 52, 522–523.
- Eslick, J.D., 2006. *Helicobacter pylori* infection causes gastric cancer? A review of the epidemiological, meta-analytic and experimental evidence. *World J. Gastroenterol.* 12, 2991–2999.
- Hostettmann-Kaldas, M., Nakanishi, M., 1979. Moronic acid a simple triterpenoid keto- acid with antimicrobial activity isolated from *Ozoroa mucronata*. *Planta Med.* 37, 358–360.
- Huweiz, F.U., Thorwell, D., Cockayne, A., Ala'Aldeen, D.A., 1998. Mastic gum kills *Helicobacter pylori*. *N. Engl. J. Med.* 346, 1946.
- Kaliora, A.C., Stathopoulou, M.G., Triantafyllidis, J.K., Dedoussis, G.V., Andikopoulos, N.K., 2007. Chios mastic treatment of patients with active Crohn's disease. *World J. Gastroenterol.* 13, 748–753.
- Kang, J.S., Wanibuchi, H., Salim, E.I., Kinoshita, A., Fukushima, S., 2007. Evaluation of the toxicity of mastic gum with 13 weeks dietary administration to F344 rats. *Food Chem. Toxicol.* 45, 494–501.
- Lai, L.H., Sung, J.J., 2007. *Helicobacter pylori* and benign upper digestive diseases. *Best Pract. Res. Clin. Gastroenterol.* 21, 261–279.
- Loughlin, M.F., Ala'Aldeen, D.A., Jenks, P.J., 2003. Monotherapy with mastic gum does not eradicate *Helicobacter pylori* infection from mice. *J. Antimicrob. Chemother.* 51, 367–371.

- Magalhaes-Queiroz, D.M., Lizza, F., 2006. Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 11 (Suppl.1), 1–5.
- Malfetrheiner, P., Megraud, F., O'Morain, C., Bazzoli, F., El-Omar, E., Graham, D., et al., 2007. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III consensus report. *Gut* 56, 772–781.
- Marone, P., Bono, L., Leone, F., Bona, S., Carretto, E., Perversi, L., 2001. Bactericidal activity of *Pistacia lentiscus* mastic gum against *Helicobacter pylori*. *J. Chemother.* 13, 611–614.
- Paraschos, S., Magiatis, P., Mitakou, S., Petraki, K., Kalliaropoulos, A., Maragkou-dakis, P., et al., 2007. *In vitro* and *in vivo* activities of Chios mastic gum extracts and constituents against *Helicobacter pylori*. *Antimicrob. Agents Chemother.* 51, 551–559.
- Perri, F., Clemente, R., Pastore, M., Quitadamo, M., Festa, V., Bisceglie, M., et al., 1998. The C¹³ urea breath test as a predictor of intragastric bacterial load and severity of *Helicobacter pylori* gastritis. *Scand J. Clin. Lab. Invest.* 58, 19–27.