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Is *Chios mastic* gum effective in the treatment of functional dyspepsia? A prospective randomised double-blind placebo controlled trial

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ABSTRACT

Background: Herbal remedies are increasingly popular for the treatment of functional dyspepsia. *Chios mastic* gum is a resinous exudate from the stem of *Pistacia lentiscus* var. *chia*. It is a traditional natural remedy used throughout the eastern Mediterranean.

The aim of this study was to assess the efficacy of *Chios mastic* gum in patients with functional dyspepsia.
Methods: One hundred and forty eight patients fulfilling Rome II criteria for functional dyspepsia were randomly assigned to receive either *Chios mastic* gum 350 mg three times daily or placebo. After 3 weeks of treatment the change from baseline in the severity of symptoms of functional dyspepsia was assessed using the Hong Kong index of dyspepsia. Patients' global assessment of efficacy was also evaluated.
Results: The symptom score after treatment was significantly lower in the *Chios mastic* gum than in the placebo group ((14.78 ± 1.78) vs (19.96 ± 1.83)) ($p < 0.05$). There was a marked improvement of symptoms in 40% of patients receiving placebo and in 77% of patients receiving *Chios mastic* gum ($p < 0.02$). Individual symptoms that showed significant improvement with *Chios mastic* gum were: stomach pain in general, stomach pain when anxious, dull ache in the upper abdomen and heartburn (<0.05 for all four symptoms).
Conclusion: Chios mastic gum significantly improves symptoms in patients with functional dyspepsia compared to placebo.

1. Introduction

Dyspepsia is a very common problem that affects large numbers of individuals worldwide especially in the Westernised world. Patients with dyspepsia problems are treated both by primary care physicians as well as gastroenterologists in the different health care systems. Dyspepsia in the absence of an identifiable structural lesion in the upper gastrointestinal system is referred to as functional dyspepsia (Talley et al., 1999).

Treatment of functional dyspepsia remains problematic. Historically the H_2-receptor antagonists have been tried in dyspepsia but the results were generally disappointing (Talley et al., 1986; Kato et al., 2005; Ashizawa et al., 2006,). At about the same time prokinetics were also used in functional dyspepsia. Mosapride showed a small improvement in symptoms in a small trial (Wu et al., 2006). Cisapride, a related compound has shown superiority over placebo in meta-analyses but its use is now severely restricted due to cardiac side effects (Veldhuyzen van Zanten et al., 2001). Itopride a newer D2-receptor antagonist has shown some promising results in one large and two smaller trials (Amarapurkar and Rane, 2004; Zhu et al., 2005; Holtmann et al., 2006) but it has failed Phase III trials (Talley et al., 2008). As for proton pump inhibitors recent meta-analyses have shown efficacy but the effect was modest (Moayyedi et al., 2004; Van Zanten et al., 2006). *Helicobacter pylori* eradication has shown some minor benefit in recent trial and meta-analyses (Moayyedi et al., 2003; Di Mario et al., 2005; Ang et al., 2006). As for alosetron, whose use is restricted in some countries due to side effects it has shown benefit in functional dyspepsia (Talley et al., 2001).

As treatment of functional dyspepsia with conventional medication remains unsatisfactory, herbal remedies such as iberogast (Melzer et al., 2004a,b; Von Arnim et al., 2007), and artichoke leaf extract (Holtmann et al., 2003; Meier and Brignoli, 2005) have been tried in small studies for the treatment of this condition. The results have been promising and results from bigger trials are awaited.

Chios mastic gum is a resinous exudate which is derived from the stem of the bush *Pistacia lentiscus* var. *chia*. *Chios mastic* gum is usually sold as a chewing gum. It is also used in cooking and

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cosmetics. There have been references to Chios mastic gum as a medicinal product for gastrointestinal upsets since ancient times (Kaliora et al., 2007). It is still widely used as a remedy for these in many parts of the Mediterranean basin and the Middle East (Triantafyllou et al., 2007).

Although *Chios mastic* gum is traditionally used in dyspepsia like symptoms no properly designed trial has ever been conducted to test its efficacy. Our aim was to evaluate the efficacy on *Chios mastic* gum in patients with functional dyspepsia in terms of improvement of the perception of symptoms.

2. Materials and methods

The trial was a 3-week double-blind randomised placebo controlled study designed to investigate the effects of *Chios mastic* gum on functional dyspepsia symptoms.

The study was conducted in Chios District General Hospital Skyliitsion, Chios, Greece.

The study was approved by the local ethics committee (Reference no. MGCGH0031/05) and the Greek Medicines Agency (Reference no CGH266/05 B). All procedures followed were in accordance with the Declaration of Helsinki (1975, amended 2000) on experimentation on human subjects. Patients that entered the study had previously given written informed consent.

2.1. Assignment

Patients visiting the Gastroenterology, Internal Medicine and Abdominal Surgery clinics at the Outpatients Department were recruited. Subjects were consecutively enrolled.

Males and females 18–75 years of age were eligible for the trial if they were found to satisfy Rome II criteria for functional dyspepsia (Talley et al., 1999). Functional dyspepsia was diagnosed if recurrent upper abdominal pain or discomfort were present. Discomfort was characterised by the presence of one or more of the following symptoms. Bloating, nausea, vomiting, belching and loss of appetite. These could be associated with gastro-esophageal reflux symptoms i.e. acid regurgitation and heartburn. Patients whose main (more than once a week) or only complain was gastro-esophageal reflux were excluded from the trial. Symptoms had to be present for at least 12 weeks in the previous 9 months.

Patients underwent a physical examination, routine laboratory tests, upper gastrointestinal endoscopy and *Helicobacter pylori* testing. Patients harbouring a *Helicobacer pylori* infection were excluded. Upper gastrointestinal endoscopy had to be performed within the last 2 months before entering the study. Patients with a hiatal hernia were allowed to enter the study but not patients who were found to have gastritis or duodenitis, on endoscopy.

Patients that were using medication that could alter gastric function notably narcotics, tricyclic antidepressants and calcium channel blockers were not eligible for the study. A washout period of 4 weeks was imposed on the use of prokinetics and proton pump inhibitors.

2.2. Masking

The randomisation was generated using Proc random (SAS version 6.9). Patients were enrolled at the Dyspepsia clinic of the Gastroenterology Department. Medication was delivered to the hospital in blocks of twelve. Central pharmacy assigned participants to their groups. Patients received one capsule three times a day for 3 weeks. The study medication was packaged identically for the two study groups and was identifiable only by a randomisation number. Patients who met the inclusion and exclusion criteria were assigned a randomisation number and were treated with the correspondingly identified study medication. Participants, researchers that conducted the study and those who assessed the outcomes were blinded to group assignment.

2.3. Participant flow

After the diagnosis of functional dyspepsia was established, patients were asked to enter the study. Between two and nine days after completion of the test battery, the disease specific questionnaire was administered to determine patients' baseline status. At that point they were randomised to receive either placebo or pure *Chios mastic* gum 350 mg three times daily for 3 weeks. Pure *Chios mastic* gum was dispensed in capsule form with no flavourings added to the natural product. Placebo capsules were identical in size and filled with lactose. Patients were asked to take tablets before meals. Quality control of the mastic gum was assured by the Mastic Gum Growers Cooperative. Composition of *Chios mastic* gum can be found in Appendix A. A reference sample from the same batch was stored by the sponsor. Mastic gum was first mechanically separated from impurities and finally, purity was checked by fractional distillation.

2.4. Analysis

We used the validated Hong Kong index of Dyspepsia (HKID) (Hu et al., 2002), to assess symptoms at baseline and at the end of treatment. The HKID was administered by an investigator in a face to face interview. It measures the following twelve dyspepsia symptoms on a five point scale each (0 for absent, 1 for mild, 2 for moderate, 3 for severe and 4 for very severe). Stomach pain in general, bloating of the upper abdomen, dull ache of the upper abdomen, stomach pain before meals, stomach pain when anxious, vomiting, nausea, belching, acid regurgitation, heartburn, acidity in the stomach, loss of appetite. A summary score of 0–48 represents the severity of the dyspeptic symptoms.

Patients' global assessment of efficacy was also evaluated at the end of the 3 weeks' trial period. The first specific question used was: "Did you see any improvement of your symptoms while on the trial medication?" Then a second question was asked: "On this five point scale which answer would more accurately describe your symptoms' improvement?" Symptom-free, marked improvement, moderate improvement, no change and deterioration. A positive response to treatment was pre-specified as improvement of at least two points in the five point Likert scale.

2.5. Follow up

At the end of the study patients returned their medication and capsules were counted. Patients taking more than 75% of the capsules were thought to be compliant. At the end of the study a physical examination was performed as well as routine laboratory tests including full blood count, liver and renal function tests and measurement of blood glucose, cholesterol, triglycerides and uric acid.

One month after study completion patients returned to the clinic and an inquiry on side effects and adverse events was then made.

The change in the summary HKID score relative to the baseline was evaluated as a primary outcome. The patients' global assessment of efficacy at the end of the study was a second primary outcome.

2.6. Statistical analysis

An intention to treat analysis was conducted on all patients randomised to therapy who received at least one dose of study medication.

Table 1
Demographics of patients in the two study groups. Time is in weeks.

	Placebo	*Chios mastic* gum
Age	46.8 (11.6)	48.8 (9.9)
Male gender	21 (28%)	22 (30%)
Female gender	53 (72%)	52 (70%)
Mean HKDI pre	23.68 (1.64)	23.27 (1.83)
Body mass index mean	22.4 (6.2)	23.1 (6.1)
Mean time since initial diagnosis	38.7 (23.5)	41.4 (36.2)
Mean time since onset of symptoms	60.1 (48.4)	55.8 (45.2)
Previous PPI therapy in last 3 months	28 (38%)	31 (42%)
Previous prokinetics in last 3 months	14 (19%)	11 (15%)

Sample sizes were determined prospectively with reference to other studies that used similar end points. A sample size of 75 patients in each study group was found satisfactory to identify a difference of 5 HKID points (20 vs 15) in response rates based on significance level of 5% and a power of 80%.

Comparisons between scores of HKID before and after the intervention were made using the Wilcoxon signed ranked tests. To test the patients' global assessment to response we used the Fisher's exact test. Results are shown as mean ± standard error of the mean.

3. Results

Two hundred and forty one patients were assessed for eligibility. Eighty-three patients were excluded for various reasons. One hundred and forty eight patients were enrolled and randomised. Seventy-four received *Chios mastic* gum and seventy-four received placebo. One patient in the active treatment was lost to follow up. Four patients (one in the active treatment group and three in the placebo group) discontinued treatment because of lack of efficacy. The first patient entered the study in January 2006 and the last follow up was completed in November 2008. Patients' demographics can be found in Table 1. There were no significant differences between baseline characteristics in the two groups.

There were no differences in HKID scores before treatment in the two groups ((23.68 ± 1.64 in the *Chios mastic* gum group) vs (23.27 ± 1.93 in the placebo group)) (p = NS). There was a significant difference at the end of treatment in HKID scores in favour of the *Chios mastic* gum treatment ((14.78 ± 1.78) vs 19.96 ± 1.83)) ($p < 0.05$).

We also performed a within groups comparison. There was significant improvement in the actively treated group ((23.68 ± 1.64) vs (14.78 ± 1.78)) ($p < 0.03$). There was no significant improvement in the placebo group ((23.27 ± 1.73) vs 19.96 ± 1.69)) ($p = 0.23$).

With regards to patients' own global assessment of efficacy, 40% (30/74) of patients showed improvement on the placebo arm, while 77% (57/74) of patients in the active treatment group showed improvement of symptoms ($p < 0.02$).

Table 2
Individual score symptoms influenced by the treatment (350 mg/tid for 3 weeks).

	Placebo	*Chios mastic* gum	p
Stomach pain	0.43 (0.03)	1.05 (0.05)	<0.05
Upper abdo bloating	0.86 (0.11)	1.13 (0.13)	NS
Upper abdo dull ache	0.23 (0.03)	0.87 (0.05)	<0.05
Stomach pain bef. meals	0.43 (0.07)	0.35 (0.05)	NS
Stomach pain anxious	0.33 (0.04)	0.91 (0.06)	<0.05
Vomiting	0.17 (0.05)	0.28 (0.04)	NS
Nausea	0.41 (0.06)	0.52 (0.08)	NS
Belching	0.84 (0.09)	0.83 (0.1)	NS
Acid regurgitation	0.52 (0.04)	0.41 (0.08)	NS
Heartburn	0.21 (0.01)	0.77 (0.03)	<0.05
Acidity in the stomach	0.43 (0.07)	0.66 (0.09)	NS
Loss of appetite	0.14 (0.05)	0.25 (0.05)	NS

Abbreviations: NS: non-significant; abdo: abdomen; bef: before.

Table 3
Symptoms of gastro-esophageal reflux influenced by the treatment (350 mg/tid for 3 weeks).

	Placebo	*Chios mastic* gum
Acid regurgitation	13/74 (18%)	11/74(15%)
Improved acid regurgitation	2/13 (15%)	8/11 (73%)
p	NS	<0.001
Heartburn	10/74 (14%)	11/74 (15%)
Improved heartburn	2/10 (20%)	7/11 (64%)
p	NS	<0.005
Heartburn and acid regurg.	9/74 (13%)	11/74 (15%)
Improved both	2/9 (22%)	10/11 (91%)
p	NS	<0.001

Abbreviation: regurg: regurgitation.

Table 2 shows the results for the twelve individual symptom scores that form part of the HKID. There were no significant differences in symptoms' improvement in eight of the twelve symptoms. Differences in stomach pain in general (1.05 ± 0.05 vs 0.43 ± 0.03), stomach pain when anxious (0.91 ± 0.06 vs 0.33 ± 0.04), heartburn (0.77 ± 0.03 vs 0.21 ± 0.01) and dull ache in the upper abdomen (0.87 ± 0.05 vs 0.23 ± 0.03) were significantly in favour of the treatment group ($p < 0.05$ for all four symptoms).

Table 3 looks at the patients who had some element of gastro-esophageal reflux in the initial assessment. Looking at the placebo group 32 patients had either acid reflux or heartburn or both and 33 patients in the treatment arm had either acid reflux or heartburn or both. Only 6 patients in the placebo group showed some improvement of their symptoms at the end of the study period, whereas 25 patients in the treatment group reported benefit from the treatment ($p < 0.01$).

No patient discontinued treatment because of adverse events. One patient in the treatment group (1.35%) complained of nausea and 1 patient in the treatment group (1.35%) complained of diarrhea. Three patients (4.05%) had upper respiratory tract infections during the course of the treatment. Four patients (5.4%) complained of flu like illnesses during the follow up period. Generally mastic gum was well tolerated by the patients.

4. Discussion

Due to the paucity of effective conventional medication for the treatment of functional disorders of the alimentary tract natural remedies and herbal preparations have been tested for these conditions during the past few years.

A few studies for the treatment of irritable bowel syndrome have confirmed some efficacy for compounds such as peppermint oil, iberogast and Chinese herbal preparations (Liu et al., 1997; Bensoussan et al., 1998; Pittler and Ernst, 1998; Madisch et al., 2004; Hussain and Quigley, 2006). It is widely accepted now that complimentary approaches to the treatment of IBS have some place in the therapeutic armamentarium of treating physicians.

Treatment of functional dyspepsia has recently been a preferential niche for natural remedies. As itopride has now failed a phase III study (Talley et al., 2008), treatment of functional dyspepsia with conventional medications remains largely empirical. As such, herbal preparations seem to be reliable alternatives in the treatment of functional dyspepsia.

In this study we assessed the effects of *Chios mastic* gum, a resinous exudate, in patients with functional dyspepsia. To our knowledge this is the first double-blind placebo controlled trial to assess the effects of this natural remedy, in functional dyspepsia. *Chios mastic* gum significantly improved the perception of symptoms in patients with functional dyspepsia over 3 weeks of treatment compared to placebo.

Chios mastic gum is considered a natural remedy. Its constituent elements have been separated. Almost 25% of its total weight is a polymer which in an acid environment becomes a runny resin which could have cytoprotectant effects in patients (Dimas et al., 2009). More than 20% of its total weight constitutes the neutral fraction which does not seem to have medicinal properties. The rest of its weight constitutes the acid fraction (Paraschos et al., 2007). In that acid fraction triterpenoid acids seem to have antimicrobial and antioxidant effects. Moronic acid seems to have antimicrobial activity against E. coli, Staphylococcus species and Ozava muconata (Hostettmann-Kaldas and Nakanishi, 1979; Koutsoudaki et al., 2005) and could be the agent responsible for the effect *Chios mastic* gum has on *Helicobacter pylori* in vitro (Huwez et al., 1998; Marone et al., 2001). Masticadienonic acid inhibits bradykinin and phospholipase A2 (Giner-Larza et al., 2002). Iso-masticadienonic acid and oleanolic acid inhibit leukotriene B4 (Giner-Larza et al., 2001). In total, 69 constituents have been isolated from pure mastic gum (Kaliora et al., 2004).

Whether these triterpenoid acids could be implicated in the effect of *Chios mastic* gum in functional dyspepsia remains to be proven. Possibly, other active substances from *Chios mastic* gum could be responsible.

This trial was designed to answer specific outcome measures, notably symptom score improvement and improvement in global assessment. Despite its relatively small sample size it achieved statistically significant results. It is worth noting that three quarters of the patients receiving *Chios mastic* gum reported improvement which is one of the best results ever obtained by a medication in a placebo controlled trial of functional dyspepsia. It was almost double the improvement in the placebo group.

If we look at individual symptoms scores all twelve improved in the treatment group compared to the baseline. If we group symptoms in three major categories, i.e. pain, reflux and fullness, patients on *Chios mastic* gum showed a greater improvement of symptoms' scores in the three symptoms of the pain group and in heartburn. Improvement of postprandial fullness was not significantly better than placebo.

One of the main limitations of the study has been that the Hong Kong Index of Dyspepsia has not been validated yet in the study population. The Hong Kong Index of Dyspepsia is relatively simple and the patient needs to answer 12 questions. It was easy to translate to Greek and the study population who was not familiar with randomised controlled trials had no difficulty in answering the simple questionnaire.

Chios mastic gum seems to be more effective in improving pain and heartburn. Although none of our patients had mainly reflux symptoms there was a significant overlap between functional dyspepsia and gastro-esophageal reflux, and *Chios mastic* gum seems to be effective in alleviating concomitant heartburn in patients with functional dyspepsia. We are unsure if the effect of *Chios mastic* gum on heartburn could be the result of a gel formed by the polymer in acid conditions (Paraschos et al., 2007) or could be a prokinetic effect of *Chios mastic* gum.

A relatively high proportion of our study subjects were women. But we feel this represents a real life scenario as it is well known that women are generally attending their physicians more often than men complaining of functional gastrointestinal problems.

In summary *Chios mastic* gum appears to be efficacious in the treatment of a common condition for which few effective therapies are currently available. Further trials are guaranteed in different study populations in order to confirm our findings. A head to head comparison with the currently available treatment options, domperidone, itopride and proton pump inhibitors could be worthwhile. Further research should also be encouraged into the identification of active substances from *Chios mastic* gum that could alleviate symptoms of functional dyspepsia.

5. Role of the funding source

This study was funded by a grant from the Mastic Gum Producers Cooperative to KJ Dabos. The study was designed by the principal investigator and the design was approved by the sponsor. The Statistics Section of the Cooperative provided statistical advice for the analysis and interpretation of the data.

Conflict of interest

KJ Dabos received travel bursaries from the sponsor. E Sfika was an employee of the sponsor during the study period. LJV, DF, GIA, GG, have nothing to declare.

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Appendix A.

Chemical composition of *Chios mastic* gum.

	Percentage of weight
1. Natural polymer poly-β-myrcene	25%
2. Masticadienonic acid	12%
3. Iso-masticadienonic acid	12%
4. Oleanonic acid	6%
5. Moronic Acid	4%
6. Masticadienolic acid	1%
7. Iso-masticadienolic acid	1%
8. Other acids	3%
9. Mastic oil	3%
10. Butyspermol	2%
11. Tirucallol	2%
12. Oleanolic aldehyde	2%
13. Oleanonic aldehyde	2%
14. Betulonal	2%
15. Caryophyllene oxide	2%
16. Masticadienolal	2%
17. Iso-masticadienolal	2%
18. Other alcooles	4%
19. Other aldehydes	8%

References

Amarapurkar, D.N., Rane, P., 2004. Randomised, double-blind, comparative study to evaluate the efficacy and safety of ganaton (itopride hydrochloride) and mosapride citrate in the management of functional dyspepsia. Journal of the Indian Medical Association 102, 735–737.

Ang, T.L., Fock, K.M., Teo, E.K., Chan, Y.H., Ng, T.M., Chua, T.S., Tan, J.Y., 2006. *Helicobacter pylori* eradication versus prokinetics in the treatment of functional dyspepsia: a randomized double-blind study. Journal of Gastroenterology 41, 647–653.

Ashizawa, N., Hashimoto, T., Miyake, T., Shizuku, T., Imaoka, T., Kinoshita, Y., 2006. Efficacy of camostat mesilate compared with famotidine for treatment of functional dyspepsia: is camostat mesilate effective? Journal of Gastroenterology and Hepatology 21, 767–771.

Bensoussan, A., Talley, N.J., Hing, M., Hing, M., Menzies, R., Guo, A., Ngu, M., 1998. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. Journal of the American Medical Association 280, 1585–1589.

Dimas, K., Hatziantoniou, S., Wyche, J.H., Pantazis, P., 2009. A mastic gum extract induces suppression of growth of human colorectal tumour xenografts in immunodefficient mice. In Vivo 23, 63–68.

Di Mario, F., Stefani, N., Dal Bona, N., Rugge, M., Pilotto, A., Cavestro, G.M., Cavallaro, L.G., Franze, A., Leandro, G., 2005. Natural course of functional dyspepsia

after *Helicobacter pylori* eradication: a seven year survey. Digestive Diseases and Science 50, 2286–2295.
Giner- Larza, E.M., Manez, S., Recio, M.C., Giner, R.M., Prieto, J.M., Cerda-Nicolas, M., Rios, J.L., 2001. Oleanonic acid a 3-oxotriterpene from Pistacia, inhibits leukotriene synthesis and has anti-inflammatory activity. European Journal of Pharmacology 428, 137–143.
Giner-Larza, E.M., Manez, S., Giner, R.M., Recio, M.C., Prieto, J.M., Cerda-Nicolas, M., Rios, J.L., 2002. Anti-inflammatory triterpenes from Pistacia terebinthus gals. Planta Medica 68, 311–315.
Holtmann, G., Adam, B., Haag, S., Collet, W., Grunewald, E., Windeck, T., 2003. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. Alimentary Pharmacology and Therapeutics 18, 1099–1105.
Holtmann, G., Talley, N.J., Liebregts, T., Adam, B., Parow, C., 2006. A placebo-controlled trial of itopride in functional dyspepsia. New England Journal of Medicine 354, 832–840.
Hostettmann-Kaldas, M., Nakanishi, K., 1979. Moronic acid, a simple triterpenoid keto acid with antimicrobial activity isolated from Ozoroa mucronata. Planta Medica 37, 358–360.
Hu, W.C., Lam, K.F., Wong, Y.H., Lam, C.L., Huli, W.M., Lai, K.C., Wong, B.C., Lam, S.K., 2002. The Hong Kong index of dyspepsia: a validated symptom severity questionnaire for patients with dyspepsia. Journal of Gastroenterology and Hepatology 17, 545–551.
Hussain, Z., Quigley, E.M.M., 2006. Systematic review: complementary and alternative medicine in the irritable bowel syndrome. Alimentary Pharmacology and Therapeutics 23, 465–471.
Huwez, F.U., Thorwell, D., Cockayne, A., Ala-Aldeen, D.A., 1998. Mastic gum kills *Helicobacter pylori*. New England Journal of Medicine 339, 1946.
Kaliora, A.C., Mylona, A., Chiou, A., Petsios, D.G., Andrikopoulos, N.K., 2004. Detection and identification of simple phenolics in *Pistacia lentiscus* resin. Journal of Liquid Chromatography and Related Technologies 27, 289–300.
Kaliora, A.C., Stathopoulou, M.G., Triantafillidis, J.K., Dedoussis, G.V., Andrikopoulos, N.K., 2007. *Chios mastic* treatment of patients with active Crohn's disease. World Journal of Gastroenterology 13, 748–753.
Kato, M., Watanabe, M., Konishi, S., Kudo, M., Konno, J., Meguro, T., Kitamori, S., Nakagawa, S., Shimizu, Y., Takeda, H., Asaka, M., 2005. Randomized, double-blind, placebo-controlled crossover trial of famotidine in patients with functional dyspepsia. Alimentary Pharmacology and Therapeutics 21, 27–31.
Koutsoudaki, C., Krsek, M., Rodger, A., 2005. Chemical composition and antibacterial activity of the essential oil and the gum of *Pistacia lentiscus var. Chia*. Journal of Agricultural and Food Chemistry 53, 7681–7685.
Liu, J.H., Chen, G.H., Yeh, H.Z., Haung, C.K., Poon, S.K., 1997. Enteric-coated peppermint oil capsule in the treatment of irritable bowel syndrome: a prospective randomized trial. Journal of Gastroenterology 332, 765–768.
Madisch, A., Holtmann, G., Plein, K., Hotz, J., 2004. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. Alimentary Pharmacology and Therapeutics 19, 271–279.
Marone, P., Bono, L., Leone, E., Bona, S., Carretto, E., Perversi, L., 2001. Bactericidal activity of *Pistacia lentiscus* mastic gum against *Helicobacter pylori*. Journal of Chemotherapy 13, 611–614.
Meier, R., Brignoli, R., 2005. Artichoke leaf extract for functional dyspepsia. Result of an open prospective multicentre phase IV trial. Schweizerische Zeitschrift Ganzhe, 216–221.
Melzer, J., Iten, F., Reichling, Saller, R., 2004a. Iberis amara L and Iberogast – results of a systematic review concerning functional dyspepsia. Journal of Herbal Pharmacotherapy 4, 51–59.
Melzer, J., Rosch, W., Reichling, J., Brignoli, R., Saller, R., 2004b. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW5 (iberogast). Alimentary Pharmacology and Therapeutics 20, 1279–1287.
Moayyedi, P., Deeks, J., Talley, N., Delaney, B., Forman, D., 2003. An update of Cochrane systematic review of *Helicobacter pylori* eradication therapy in non-ulcer dyspepsia: resolving the discrepancy between systematic reviews. American Journal of Gastroenterology 98, 2621–2626.
Moayyedi, P., Delaney, B., Vakil, N., Forman, D., Talley, N.J., 2004. The effect of proton pump inhibitors in non-ulcer dyspepsia: a systematic review and economic analysis. Gastroenterology 127, 1329–1337.
Paraschos, S., Magiatis, P., Mitakou, S., Petraki, K., Kalliaropoulos, A., Maragkoudakis, A., Mentis, A., Sgouras, D., Skaltsounis, A.-L., 2007. In vitro and in vivo activities of chios mastic gum extracts, and constituents against *Helicobacter pylori*. Antimicrobial Agents and Chemotherapy 51, 551–559.
Pittler, M.H., Ernst, E., 1998. Peppermint oil for irritable bowel syndrome: a critical view and meta-analysis. American Journal of Gastroenterology 93, 1131–1135.
Talley, N.J., McNeil, D., Hayden, A., Piper, W., 1986. Randomized double – blind, placebo-controlled crossover trial of cimetidine and pirenzepine in nonulcer dyspepsia. Gastroenterology 91, 149–156.
Talley, N.J., Stanghellini, V., Heading, R.C., Koch, K.L., Malagelada, J.R., Tytgat, G.N.J., 1999. Functional gastroduodenal disorders. Gut II, 37–42.
Talley, N.J., Van Zanten, S.V., Saez, L.R., Dukes, G., Pershy, T., Heath, M., Kleoudis, C., Mangel, A.W., 2001. A dose-ranging placebo-controlled, randomized trial of alosetron in patients with functional dyspepsia. Alimentary Pharmacology and Therapeutics 15, 525–537.
Talley, N.J., Tack, J., Ptak, T., Gupta, R., Giguere, M., 2008. Itopride in functional dyspepsia: results of two phase III multicenter, randomized, double-blind, placebo-controlled trials. Gut 57, 740–746.
Triantafyllou, A., Chaviaras, N., Sergentanis, T.N., Protopapa, E., Tsaknis, J., 2007. Chios mastic gum modulates serum biochemical parameters in a human population. Journal of Ethnopharmacology 11, 43–47.
Van Zanten, S.V., Armstrong, D., Chiba, N., Flook, N., White, R.J., Chakraborty, B., Gasco, A., 2006. Esomeprazole 40 mg once a day in patients with functional dyspepsia: the randomized, placebo-controlled ENTER trial. American Journal of Gastroenterology 101, 2096–2106.
Veldhuyzen van Zanten, S.J., Jones, M.J., Verlinden, M., Talley, N.J., 2001. Efficacy of cisapride and domperidone in functional (non-ulcer) dyspepsia: a meta-analysis. American Journal of Gastroenterology 96, 689–696.
Von Arnim, U., Peitz, U., Vinson, B., Gundermann, K.J., Malfertheimer, P., 2007. STW 5 a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. American Journal of Gastroenterology 102, 1268–1275.
Wu, Z.Y., Wang, Y.P., Chao, Z., 2006. Mosapride for functional dyspepsia: a systematic review. Chinese Journal of Evidence Based Medicine 6, 790–803.
Zhu, C.Q., Mao, Y.M., Zeng, M.D., 2005. Clinical study of itopride hydrochloride on treatment of functional dyspepsia. Journal of China Pharmaceutical University 36, 580–583.