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ORIGINAL ARTICLE

Effectiveness of a nutraceutical supplement containing highly standardized perilla and ginger extracts in patients with functional dyspepsia

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ABSTRACT

BACKGROUND: In Western countries functional dyspepsia (FD) has a prevalence of 10-20% among adults and although many drugs are currently available for use within clinical practice, FD remains an important challenge for physicians. Recently, food supplements that are ginger-based, along with other botanicals, have been proposed to be a possible natural alternative to pharmaceutical drugs to empirically counteract the symptoms of FD.

METHODS: We have therefore retrospectively analyzed the efficacy and safety profiles of a nutraceutical containing, in addition to a highly standardized ginger root extract, a multi-fractionated botanical obtained from *Perilla frutescens* leaf containing an innovative bouquet of compounds, including hydrophilic polyphenols and the lipophilic terpenoid perilla ketone.

RESULTS: The results of our single-group study, obtained from patients with a diagnosis of FD who were treated with the perilla/ginger nutraceutical, demonstrated a good efficacy profile, with a significant reduction observed in nearly all evaluated symptoms (epigastric pain, heartburn, gastric reflux, nausea, borborygmi, early satiety, diarrhea/constipation) starting from the first week of treatment that was further improved after 2 weeks. The treatment was well tolerated with very mild side effects (flatulence, meteorism, gastric burning, difficulty in falling asleep) lasting 3–4 days, which disappeared without stopping the treatment.

CONCLUSIONS: Despite all the limitations of our pragmatic study, we believe that the perilla and ginger supplement we have used can be considered a valid tool for an empirical approach to treating patients with FD, especially when a non-conventional drug treatment is preferable to the patient and considered suitable by the physician.

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KEY WORDS: Perilla frutescens; Pain; Dyspepsia.

Functional dyspepsia (FD) is a clinical syndrome characterized by persistent or recurrent upper abdominal symptoms, such as epigastric pain, postprandial fullness, and early satiety, in the absence of any organic explanation.[1] Based on the Rome III criteria, FD is commonly divided into postprandial distress syndrome (PDS), characterized by postprandial fullness and early satiation, and epigastric pain syndrome (EPS), characterized by epigastric pain and burning.[2] In Western countries, FD prevalence is reported to be between 10% and 20% in the adult population;[3] higher values (>40%) are reached in the industrialized Eastern countries.[4] The etiopathogenesis of FD is certainly multifactorial, and is described in detail elsewhere.[5] Although many drugs are currently available for use in clinical practice, FD remains a consider-

able challenge partly because two of the main classes of compounds used with proven clinical efficacy, prokinetics and proton pump inhibitors, have generated some doubts in terms of the benefit-risk ratio.[6, 7] For this reason, several ginger-based food supplements have been proposed as being possible natural alternatives to empirically counteract symptoms of FD.[8, 9] Ginger, from a mechanistic perspective, is claimed to be effective against some symptoms commonly used to describe dyspepsia, for instance, nausea and vomiting, probably due to a weak inhibitory effect on muscarinic cholinergic M_3 and serotonergic 5-HT_3 receptors.[10] Ginger has also been reported to counteract motion sickness by preventing the development of gastric dysrhythmias and the elevation of plasma vasopressin.[11] These mechanisms of action are thought to be mediated by gingerols and shogaols present in ginger,[12] and could perhaps explain the possible positive role of ginger extract in treating FD as well as some other functional gastrointestinal diseases.[13] Since ginger appears to demonstrate greater clinical efficacy in the relief of stomach rather than intestinal discomfort, researchers are continuously looking for new botanicals that are more effective with respect to gut motility.[14] *Perilla frutescens* leaves are commonly used as a food in many Asian countries.[15] Water extract obtained from *Perilla frutescens* leaves has been reported to contain mainly apigenin, luteolin, rosmarinic acid, and their conjugate derivates, including vicenin-2,[16] and has been demonstrated, *in vitro*, *in vivo*, and clinically, to be endowed with prokinetic, antispasmodic, and anti-inflammatory effects.[17-19] In contrast, essential oil from perilla leaves contains perilla ketone, a monoterpenoid capable of exerting a clear intestinal propulsion effect in mice.[20] Recently, a multi-fractionated extract from perilla leaves, containing both the hydrophilic and the lipophilic active components, has been developed and then formulated in a finished product along with a highly standardized ginger root extract.[21] Our study is therefore a retrospective analysis of our pragmatic and routine clinical practice when treating patients with signs and symptoms of FD, to whom we have suggested the use of this perilla/ginger supplement for a certain period before proceeding, in cases of an absence of clinical response, with endoscopic evaluation.

Materials and methods

Study design and aim

Our study encompassed a retrospective analysis of the data obtained from our pragmatic and routine procedures conducted in the Digestive Endoscopy Dept. at Ceva Hospital (Italy) between March and July 2019. The aim of the study was to investigate the role played by a perilla/ginger-based nutraceutical product in counteracting signs and symptoms of FD. All patient data were completely anonymized and the study was performed in accordance with the ethical standards established by the Declaration of Helsinki and by the local (CN) institutional committee. Despite the retrospective and anonymized features of the study, all patients provided signed informed consent to publish the results.

Patient selection

According to the guidelines, subjects (>18 years old) considered eligible for our retrospective analysis were those diagnosed as being affected by FD (according to Rome III criteria) who agreed to a pragmatic "test and treat" approach with the perilla/ginger supplement before proceeding, in cases of an absence of clinical response, with endoscopic evaluation and further *Helicobacter pylori* testing.[22] The exclusion criteria were: a history of gastrectomy, organic brain disease, schizophrenia or a predisposition to schizophrenia, alcoholism or any other substance abuse disorder, serious hormonal imbalance (for example, hyperthyroidism), serious heart, liver, kidney, or hematopoietic disease, and a history of hypersensitivity to active or excipient agents possibly contained within the tested formula. In addition, pregnant or lactating women, women who could have conceived or hoped to conceive during the study period, and other potential subjects deemed unsuitable by the physician, could not take part in the study. Use of concomitant medications that could have interacted with the test agents, or affect evaluation of the clinical ef-

fects (prokinetic, antiulcer, and anticholinergic agents) was not allowed. If medications of this type were used prior to study entry, a wash-out period of at least 7 days was mandated before study commencement.

Analyzed parameters

As the primary endpoint, subjects were asked to evaluate their own symptoms at baseline and after 1 and 2 weeks of treatment by completing a questionnaire reporting the trend (on a scale between 0: not at all affected, and 7: unbearably affected) of gastric and gut symptoms including epigastric pain, heartburn, gastric reflux, nausea, borborygmi, early satiety, and diarrhea/constipation. Secondary endpoints were tolerability (scale: 0-10), declared adherence (%), and side effects (number of subjects and type of side effect observed in the period of treatment) associated with the therapy.

Treatment and product

Patients were recommended to use as a unique treatment a perilla/ginger nutraceutical, administered for 14 days, twice a day, 30 minutes before lunch and dinner. The product used was Dispepril® enteric-coated tablets. Each tablet contains 150 mg of a multi-fractionated extract from *Perilla frutescens* leaves, and 375 mg of *Zingiber officinalis* root extract, standardized to contain not less than 22% gingerols and shogaols. The product is manufactured by Labomar (Istrana, VC, Italy) and traded by Pharmextracta (Pontenure, PC, Italy). The product was notified to the Italian Health Authorities in 2018, November 20th.

Statistical analysis

The difference in terms of outcome was determined using the two-tailed Wilcoxon–Mann–Whitney test. The statistical software used was JMP 10 for Mac OsX and the threshold for statistical significance was 95%.

Results

Our study comprised a single-group, retrospective evaluation of the findings obtained from our pragmatic and routine clinical practice in managing adult subjects with FD. Between March and July 2019, we treated 75 subjects reporting symptoms of possible FD. According to our experience, expertise, and medical visit results, we proposed a pragmatic "test and treat" approach to 69 of these subjects, and received a positive agreement from 65 individuals. For 7 of these we observed a complete lack of response after the first week of treatment, and therefore, after stopping the treatment, these patients were subjected to further analysis (an endoscopy procedure, and in cases where necessary, additional *H. pylori* testing). The results of our analysis are based therefore on 58 patients. In Table I, subject demographic and medical characteristics are shown. In Table II the symptom trends are reported. A very significant trend was observed with respect to epigastric pain and nausea, used to score and clinically classify patients with EPS,[23] with a reduction of about 80 and 90%, respectively, in the scores *versus* baseline. Borborygmi and early satiety, used to score and clinically classify subjects with PDS,[23] were significantly reduced by more than 70% *versus* baseline. Smaller reductions of approximately 30 and 60%, respectively, were observed for heartburn and gastric reflux, compared to baseline. Diarrhea or constipation scores, indicative of bowel discomfort, showed a reduction of approximately 70%. Notably, in our study, subjects with constipation, classified as

TABLE I.—*Demographic and clinical and treatment characteristics of the analyzed patients (N.=58).*

Age (years)	54.4±12.8
Age range (years)	23-79
Sex (males/females)	24/34
BMI (kg/m^2)	22.6±3.3
H. pylori status (positive/negative/unknown)	9/5/44
Time from first diagnosis (years)	2.2±2.8
Medication (or self-medication) for FD in the past (yes/no)	21/37
Therapy already used in the past	
Proton pump inhibitors	7
H2 receptor antagonists	5
Prokinetics (drugs)	4
Alginic acids	3
Botanicals/supplements	2
FD subgroup (EPS/PDS/overlapping)	28/20/10

Age, BMI, and time from first diagnosis are shown as the average±standard deviation.
BMI: Body Mass Index; FD: functional dyspepsia; EPS: epigastric pain syndrome; PDS: postprandial distress syndrome.

TABLE II.—*Trends in symptom scores (average ± standard deviation) at baseline and after 1 and 2 weeks of treatment, and the percentage change between baseline and the score registered at the end of the second week.*

Symptom	Baseline	1st week	2nd week	Δ
Epigastric pain	5.4±2.8	3.4±2.2°	1.2±0.8°°	-78.8%
Heartburn	2.3±1.6	1.9±2.0	1.5±1.5°	-34.8%
Gastric reflux	1.5±0.8	0.4±0.7°°	0.5±0.6°°	-66.6%
Nausea	5.6±1.7	1.4±1.3°°	0.4±0.2^	-92.8%
Borborygmi	5.1±1.4	2.5±1.5°	1.4±1.6°°	-72.5%
Early satiety	4.4±0.9	1.4±0.7°°	1.3±0.7°°	-70.5%
Diarrhea/constipation	4.7±1.4	1.7±1.8°°	1.5±1.3°°	-68.1%

°P<0.05 *vs.* baseline; °°P<0.01 *vs.* baseline; ^P<0.001 *vs.* baseline.

TABLE III.—*Tolerability (average ± standard deviation), adherence (%), and side effects (number of subjects/total subjects) associated with therapy with a perilla/ginger-based supplement as evaluated at the end of treatment (2 weeks).*

Tolerability	8.3±0.9
Adherence	>95%
Side effects*	12/58

*Seven subjects reported flatulence and/or meteorism as the main side effect lasting for 4 days; 3 subjects reported an increase in gastric burning (in the first 4 days); and 2 subjects reported difficulty in falling asleep (in the first 3 days).

mild to moderate, numbered 38, which is much greater than the number of subjects with mild to moderate diarrhea that came to 15. Five subjects declared they had no bowel discomfort (data not shown). Finally, the secondary endpoints are reported in Table III. Tolerability was very good and the declared adherence to therapy was very high. Side effects affected 12 (out of 58) patients. Seven subjects reported flatulence and/or meteorism as the main side effect for the first 4 days; 3 subjects reported an increase in gastric burning (in the first 4 days); and 2 subjects reported difficulty in falling asleep (in the first 3 days).

Discussion

This retrospective study represents our highly pragmatic approach to treating FD in a cohort of 58 patients receiving a perilla/ginger-based supplement. The algorithm commonly used to treat patients with suspected FD envisages a "test and try" attempt to counteract symptoms as a possible initial approach. Proton pump inhibitors and/or prokinetics are clearly the first options in such an approach.[24-26] Recently, several supplements have been proposed to medical practitioners and specialists in gastroenterology that are mainly based on ginger extracts. Commonly added ingredients, included to increase the effectiveness of ginger, are artichoke and/or aloe extracts, alginic acid (also available at certain dosages within the dietary supplement sector, at least in Europe), and other herbal or spice components.[27] In our routine practice, we recently started using a product made by the association of ginger extract with an innovative multi-fractionated *Perilla frutescens* leaf extract. Indeed, a plethora of active compounds can be extracted from perilla leaves, all of which are effective in counteracting the gastric and bowel symptoms of FD or that can even show anticancer properties.[28] The results of our study demonstrate the significant efficacy of the perilla/ginger combination with respect to all of the symptoms used to describe the dyspeptic syndrome. Observed side effects were extremely mild and did not necessitate the termination of treatment for any patient. The highly significant results obtained regarding epigastric pain/nausea and borborygmi/early satiety, symptoms respectively describing patients with EPS and PDS, reflects our diagnostic hypothesis at the time of enrolment when we assumed that 28 and 20 subjects each suffered from EPS and PDS, respectively, with 10 subjects showing overlapping symptomatology (Table I).

Limitations of the study

We are aware that our single-group, retrospective study has limitations. First of all, this has not been a prospective, randomized, double-blind, placebo-controlled clinical trial where the results would certainly carry more weight. Second, our analysis does contain some important bias. For

instance, we did not control any aspect of diet. Moreover, our observation lasted for only two weeks and we did not evaluate what happens during a possible wash-out. Finally, our observations have been conducted on only 58 patients.

Conclusions

Despite all these, and perhaps more limitations, we believe that our study allows us to confirm the efficacy of ginger-based formulas, as reported by many authors, in counteracting to a good extent the symptoms of FD. Moreover, our analysis suggests a possible add-on effect of the perilla leaves extract, particularly regarding the extract used declared to contain two different fractions (hydro- and liposoluble). In conclusion, an appropriate dose of highly standardized ginger extract along with a multi-fractionated perilla extract administered twice a day can be considered a valid tool for a pragmatic approach to treating patients with FD, especially when a non-conventional drug therapy is preferred by the patient and considered suitable by the physician.

References

1. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006;130:1377–90.

2. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, *et al.* Functional gastroduodenal disorders. Gastroenterology 2006;130:1466–79.

3. Zagari RM, Law GR, Fuccio L, Cennamo V, Gilthorpe MS, Forman D, *et al.* Epidemiology of functional dyspepsia and subgroups in the Italian general population: an endoscopic study. Gastroenterology 2010;138:1302–11.

4. Okumura T, Tanno S, Ohhira M, Tanno S. Prevalence of functional dyspepsia in an outpatient clinic with primary care physicians in Japan. J Gastroenterol 2010;45:187–94.

5. Camilleri M. Functional dyspepsia: mechanisms of symptom generation and appropriate management of patients. Gastroenterol Clin North Am 2007;36:649–64, xi–x.

6. Fife D, Waller J, Kaplan S, Hu P, Phillips S, Oliveria SA, *et al.* Awareness of, and compliance with, domperidone revised labeling after a risk-minimization activity in Europe. Clin Drug Investig 2019;39:1057–66.

7. Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks. Nat Rev Gastroenterol Hepatol 2017;14:697–710.

8. Lazzini S, Polinelli W, Riva A, Morazzoni P, Bombardelli E. The effect of ginger (Zingiber officinalis) and artichoke (Cynara cardunculus) extract supplementation on gastric motility: a pilot randomized study in healthy volunteers. Eur Rev Med Pharmacol Sci 2016;20:146–9.

9. Pellicano R, Ribaldone DG, Saracco GM, Leone N, De Angelis C, Arrigoni A, *et al.* Benefit of supplements in functional dyspepsia after treatment of Helicobacter pylori. Minerva Gastroenterol Dietol 2014;60:263–8.

10. Pertz HH, Lehmann J, Roth-Ehrang R, Elz S. Effects of ginger constituents on the gastrointestinal tract: role of cholinergic M3 and serotonergic 5-HT3 and 5-HT4 receptors. Planta Med 2011;77:973–8.

11. Lien HC, Sun WM, Chen YH, Kim H, Hasler W, Owyang C. Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circular vection. Am J Physiol Gastrointest Liver Physiol 2003;284:G481–9.

12. Giacosa A, Morazzoni P, Bombardelli E, Riva A, Bianchi Porro G, Rondanelli M. Can nausea and vomiting be treated with ginger extract? Eur Rev Med Pharmacol Sci 2015;19:1291–6.

13. Nikkhah Bodagh M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: A systematic review of clinical trials. Food Sci Nutr 2018;7:96–108.

14. Algieri F, Rodriguez-Nogales A, Rodriguez-Cabezas ME, Risco S, Ocete MA, Galvez J. Botanical drugs as an emerging strategy in inflammatory bowel disease: a review. Mediators Inflamm 2015;2015:179616.

15. Kwak Y, Ju J. Inhibitory activities of Perilla frutescens britton leaf extract against the growth, migration, and adhesion of human cancer cells. Nutr Res Pract 2015;9:11–6.

16. Yu H, Qiu JF, Ma LJ, Hu YJ, Li P, Wan JB. Phytochemical and phytopharmacological review of Perilla frutescens L. (Labiatae), a traditional edible-medicinal herb in China. Food Chem Toxicol 2017;108(Pt B):375–91.

17. Buchwald-Werner S, Fujii H, Reule C, Schoen C. Perilla extract improves gastrointestinal discomfort in a randomized placebo controlled double blind human pilot study. BMC Complement Altern Med 2014;14:173.

18. Urushima H, Nishimura J, Mizushima T, Hayashi N, Maeda K, Ito T. Perilla frutescens extract ameliorates DSS-induced colitis by suppressing proinflammatory cytokines and inducing anti-inflammatory cytokines. Am J Physiol Gastrointest Liver Physiol 2015;308:G32–41.

19. Verspohl EJ, Fujii H, Homma K, Buchwald-Werner S. Testing of Perilla frutescens extract and Vicenin 2 for their antispasmodic effect. Phytomedicine 2013;20:427–31.

20. Koezuka Y, Honda G, Tabata M. An intestinal propulsion promoting substance from Perilla frutescens and its mechanism of action. Planta Med 1985;51:480–2.

21. Nannoni G, Mattarocci A, Volterrani G, Alì A, Di Pierro F. Development of a double-fractionated Perilla frutescens leaf extract and its possible use in functional dyspepsia. Nutrafoods 2018;17:83–8.

22. Feldman M, Friedman L, Brandt L. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Eighth edition. Philadelphia: Saunders Elsevier; 2018.

23. Kamiya T, Shikano M, Kubota E, Mizoshita T, Wada T, Tanida S, *et al.* A multicenter randomized trial comparing rabeprazole and itopride in patients with functional dyspepsia in Japan: the NAGOYA study. J Clin Biochem Nutr 2017;60:130–5.

24. Gisbert JP, Calvet X, Ferrándiz J, Mascort J, Alonso-Coello P, Marzo M. Sociedad Española de Medicina de Familia y Comunitaria. Clinical practice guideline on the management of patients with dyspepsia. Update 2012. Gastroenterol Hepatol 2012;35:725.e1–38.

25. Giurcan R, Voiosu TA. Functional dyspepsia: a pragmatic approach. Rom J Intern Med 2010;48:9–15.

26. Ford AC, Moayyedi P. Managing dyspepsia. Curr Gastroenterol Rep 2009;11:288–94.

27. Fifi AC, Axelrod CH, Chakraborty P, Saps M. Herbs and spices in the treatment of functional gastrointestinal disorders: a review of clinical trials. Nutrients 2018;10:1715.

28. Kagawa N, Iguchi H, Henzan M, Hanaoka M. Drying the leaves of Perilla frutescens increases their content of anticancer nutraceuticals. Food Sci Nutr 2019;7:1494–501.

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