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# The effect of ginger *(Zingiber officinalis)* and artichoke *(Cynara cardunculus)* extract supplementation on gastric motility: a pilot randomized study in healthy volunteers

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**Abstract. – OBJECTIVE: Prodigest® is the standardized combination of artichoke and ginger extracts. This combination was safe and effective in the treatment of functional dyspepsia. However, further evidence could be useful to shed new lights on the effect of Prodigest® on gastric motility. This pilot randomized study on healthy volunteers investigates the prokinetic activity of Prodigest®.**

**SUBJECTS AND METHODS: This was a randomized, cross-over study in healthy volunteers comparing Prodigest® versus placebo. Eleven healthy volunteers were enrolled. Each participant underwent two evaluations, at a 7-day interval. Ten minutes before the main meal, the baseline area of gastric volume was determined by ultrasonography. The subject was then given one Prodigest® or placebo capsule and, then consumed a standardized meal. One hour after the meal, the gastric volume was measured again. Two weeks after the second evaluation, three subjects repeated the above-mentioned procedures taking two capsules of Prodigest®.**

**RESULTS: The mean gastric area at baseline was 3.2±0.5 cm$^2$; after the meal, this figure was 8.4±0.7 cm$^2$ with Prodigest® and 11.0±1.5 cm2 with placebo ($p$<0.001). The after-meal gastric area was significantly smaller, with a -24% difference, following the combination of extracts, as compared with placebo ($p$<0.001). The effect of two capsules of Prodigest® seems to be more evident but due to the very small number of the patients sample further clinical data are necessary before confirming the dose-related effects.**

**CONCLUSIONS: This pilot study shows that Prodigest®, a standardized extract of ginger and artichoke, significantly promotes gastric emptying in healthy volunteers without being associated with notable adverse effects.**

*Key Words:*
Zingiber officinalis, Cynara cardunculus, Functional dyspepsia.

## Introduction

The prokinetic effect of ginger (*Zingiber officinalis*) has been shown in a number of studies and it is now extensively recognized[1,2]. This plant has long been used in Chinese and Indian traditional medicine to treat gastrointestinal disorders such as indigestion, flatulence, fever, nausea and vomiting[1]. Ginger is also used for the treatment of nausea in pregnant women or after surgical interventions, as well as in the prevention and treatment of chemotherapy-induced nausea and vomiting[1,3-5].

Prodigest® is the patented (WO 2010/083968) standardized combination of an hydro-alcoholic extract from artichoke leaves (*Cynara cardunculus*) and the lipophilic extract from ginger roots. It has been suggested that the extract of *Cynara cardunculus* can complement the effects of ginger, since the former is active on small bowel while the latter on stomach[6]. This combination was safe and effective in the treatment of functional dyspepsia, as demonstrated by a recent randomized placebo controlled study on 126 patients[6]. However, further evidence appears required to shed new lights on the effect of this combination on gastric motility[6].

We, therefore, conducted a pilot randomized study on healthy volunteers, in order to perform additional investigations on the prokinetic activity of Prodigest® and to preliminary evaluate its potential in the treatment of gastrointestinal conditions such as functional dyspepsia.

## Subjects and Methods

### Design and Subjects

This was a randomized, cross-over study in healthy volunteers comparing Prodigest® capsules



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(Indena SpA, Milan, Italy) versus placebo. The composition of Prodigest® is as follows: Artichoke leaves, dry extract 100 mg; ginger extract $CO_2$ 20 mg; dicalcium phosphate 128.3 mg; microcrystalline cellulose 58 mg; croscaramellose sodium 9 mg; silica bioxide 3.2 mg; magnesium stearate 1.5 mg.

Eleven healthy volunteers of either gender, aged 20-60 were enrolled. All subjects had to meet the following eligibility criteria: no smoking habit; no current pharmacological therapy; body mass index 18.5-24.9 kg/m$^2$; no history of abdominal surgery; no known allergy to any of the combination components.

### Procedures

Each participant underwent two evaluations, at a 7-day interval (Figure 1). Each evaluation was performed as follows: 10 minutes before the usual time of the main meal, the baseline area of gastric volume was determined by ultrasonography (Eucote Mod. Technos, 3.5 MHz probe) at the superior mesenteric artery. The subject was then given one Prodigest® or an identical placebo capsule, according to a randomization table generated by a computer. The participant consumed a standardized meal (tomato pasta, 100 g; grilled meat, 100 g; chicory with oil and salt, 20 mg; orange juice, 300 g). One hour after the meal, the gastric volume was measured again. Gastric emptying was defined as the variation in gastric volume between baseline and one hour after the meal. The participants were asked to report any adverse event occurring during the procedures or during the interval between them.

Two weeks after the completion of the second evaluation, three subjects repeated the above-mentioned procedures taking two capsules of Prodigest®.

### Statistical Analysis

Data were analyzed by descriptive statistics. Intra- and inter-group comparisons were conducted using the Student's *t*-test, with a $p$ value <0.05 considered statistically significant. All analyses

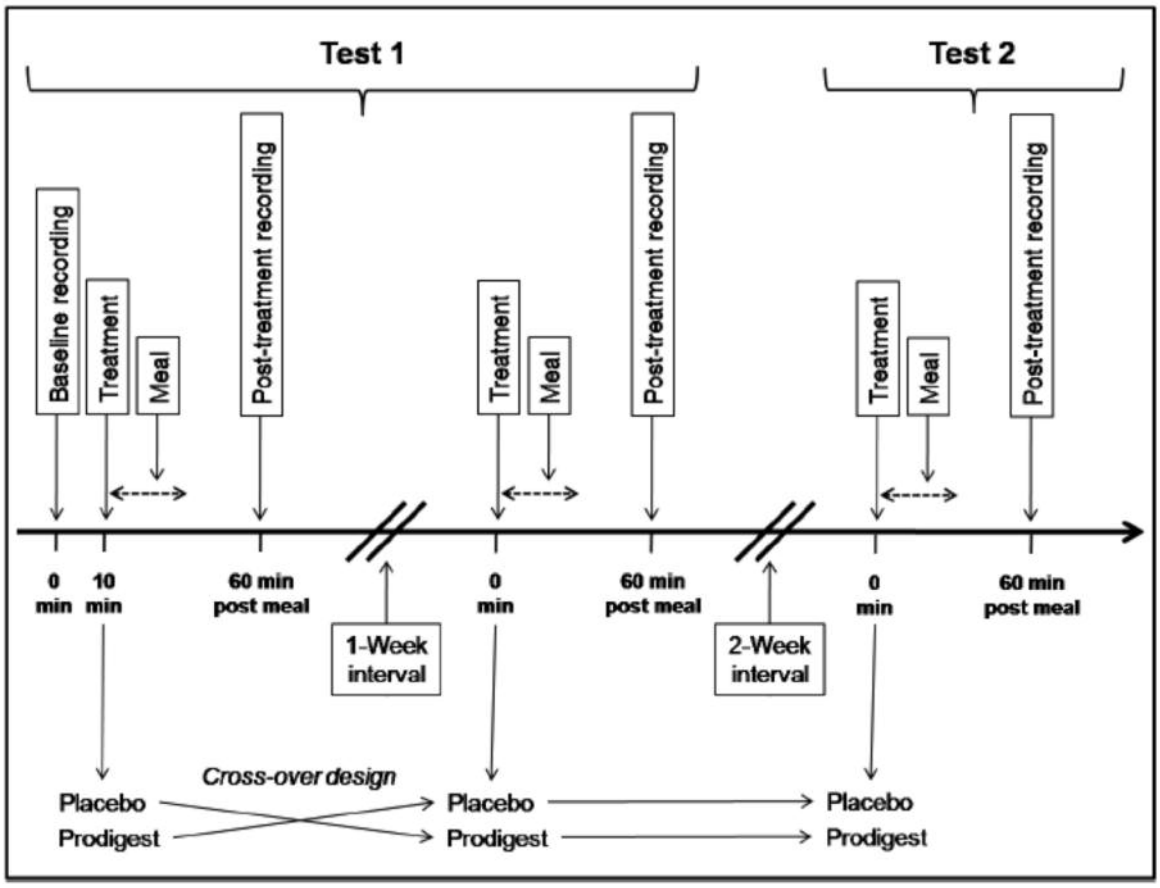


**Figure 1.** Study design.

were performed using GraphPad Prism software (GraphPad Software, La Jolla, CA, USA).

## Results

The mean age of the enrolled subjects was 41±11 years; 5 subjects (42%) were males. Table I summarizes the variation in gastric area between baseline and after-meal evaluation: the mean gastric area at baseline was 3.2±0.5 $cm^2$; after the meal, this figure was 8.4±0.7 $cm^2$ with Prodigest® and 11.0±1.5 $cm^2$ with placebo ($p$<0.001 for both comparisons). The after-meal gastric area was significantly smaller, with a -24% difference, following the combination of extracts, as compared with placebo ($p$<0.001).

Overall similar results were reported when the subject took two capsules of Prodigest®, instead of one (Table II). The effect of two capsules of Prodigest® was even more evident than with one single capsule: the difference in after-meal gastric area with the combination of extracts, as compared with placebo, was 38%. No statistical tests were possible in this case, due to the limited number of patients.

No adverse events were reported, either with a single capsule or two capsules of Prodigest®.

## Discussion

This pilot study, conducted with a randomized, cross-over design, shows that Prodigest®, a combination of standardized extracts of ginger and artichoke, significantly promotes gastric emptying in healthy volunteers after the consumption of a standardized meal without being associated with notable adverse effects. Impaired gastric emptying is a well-recognized contributor to the pathophysiology of gastrointestinal conditions like functional dyspepsia[7] and nausea[8]. Noteworthy, the use of nutritional supplementation for the treatment of these conditions has been extensively suggested[1,9]. However, the use of well-standardized, well-characterized and highly reproducible extracts is recommended over the administration of less-standardized ones or those for which less robust scientific evidence is available[10-13].

The results of the present study lend further support to the evidence provided by a recent

**Table I.** Variation in gastric area between baseline and after-meal evaluation with one capsule of either Prodigest® or placebo.

| Patient (age, gender) | Baseline ($cm^2$) | After meal, Prodigest® ($cm^2$) | After meal, placebo® ($cm^2$) | Difference between Prodigest and placebo® (%) |
|---|---|---|---|---|
| 1 (60, F) | 3.2 | 9.4 | 12.6 | 25.0 |
| 2 (55, F) | 2.5 | 7.6 | 8.2 | 7.5 |
| 3 (28, F) | 3.4 | 8.6 | 11.4 | 24.4 |
| 4 (34, M) | 3.7 | 8.4 | 12.1 | 31.4 |
| 5 (45, F) | 2.8 | 7.4 | 10.5 | 30.6 |
| 6 (46, F) | 3.2 | 7.5 | 9.6 | 22.1 |
| 7 (39, M) | 3.0 | 8.6 | 10.5 | 19.9 |
| 8 (48, M) | 3.3 | 8.9 | 9.4 | 6.4 |
| 9 (41, M) | 4.2 | 9.4 | 12.6 | 26.4 |
| 10 (24, M) | 3.6 | 8.9 | 13.4 | 34.6 |
| 11 (32, F) | 3.0 | 8.0 | 11.5 | 30.4 |
| Mean±SD | 3.2 ± 0.5 | 8.4 ± 0.7* | 11.0 ± 1.5* | 24 ± 9+ |

*$p$<0.001 vs. baseline; +$p$<0.001 for Prodigest vs. placebo.

**Table II.** Variation in gastric area between baseline and after-meal evaluation with two capsules of Prodigest®.

| Patient (age, gender) | Baseline ($cm^2$) | After meal, Prodigest® ($cm^2$) | After meal, placebo® ($cm^2$) | Difference between Prodigest and placebo® (%) |
|---|---|---|---|---|
| 1 (60, F) | 3.2 | 6.9 | 12.6 | 45.3 |
| 2 (55, F) | 2.5 | 6.3 | 8.2 | 23.2 |
| 3 (28, F) | 3.4 | 6.1 | 11.4 | 46.1 |
| Mean±SD | 3.0±0.4 | 6.4±0.4 | 10.7±2.2 | 38±13 |

randomized, 4-week trial on functional dyspepsia patients by Giacosa et al[6]. In more detail, 65 patients received Prodigest® and 61 placebo. After 14 days of treatment, only the supplementation group showed a significant amelioration of functional dyspepsia symptoms; this advantage was persistent until the end of the study. With respect to that previous trial, the present focused on gastric emptying by applying a validated method[14]. In addition, it suggests a dose-dependent effect of Prodigest®, without a worsening of the safety profile.

These effects on gastric emptying are mostly dependent upon the peculiar molecular actions of the ginger extract. Gastric hypomotility involves a temporary dysfunction of the integrated network of cholinergic M3 and serotonergic 5-HT3/5-HT4 receptors. The major chemical constituents of the ginger roots lipophilic extracts such as [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol do modulate all these receptors[6]. On the other hand, this specific effect on gastric motility is paralleled by the complementary actions exerted by the artichoke extract, anti-spasmodic and choleretic in particular, which result in a full pharmacological activity when tested in subjects with functional dyspepsia[1].

## Conclusions

Prodigest® facilitates gastric emptying probably in a dose-dependent manner. Despite that this is only a small pilot trial in healthy volunteers, it may pave the way for future, larger studies in patients affected from gastrointestinal conditions.

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### Conflict of Interest

The Authors declare that they have no conflict of interests.

## References

1) 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: 1291-1296.
2) Ghayur MN, Gilani AH. Pharmacological basis for the medicinal use of ginger in gastrointestinal disorders. Dig Dis Sci 2005; 50: 1889-1897.
3) Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J 2014; 13: 20.
4) Dabaghzadeh F, Khalili H, Dashti-Khavidaki S. Ginger for prevention or treatment of drug-induced nausea and vomiting. Curr Clin Pharmacol 2014; 9: 387-394.
5) Marx WM, Teleni L, McCarthy AL, Vitetta L, McKavanagh D, Thomson D, Isenring E. Ginger (Zingiber officinale) and chemotherapy-induced nausea and vomiting: a systematic literature review. Nutr Rev 2013; 71: 245-254.
6) Giacosa A, Guido D, Grassi M, Riva A, Morazzoni P, Bombardelli E, Perna S, Faliva MA, Rondanelli M. The effect of ginger (Zingiber officinalis) and artichoke (Cynara cardunculus) extract supplementation on functional dyspepsia: a randomised, double-blind, and placebo-controlled clinical trial. Evid Based Complement Alternat Med 2015; 2015: 915087.
7) Di Stefano M, Miceli E, Mazzocchi S, Tana P, Corazza GR. The role of gastric accommodation in the pathophysiology of functional dyspepsia. Eur Rev Med Pharmacol Sci 2005; 9 (5 Suppl 1): 23-28.
8) Sanger GJ, Broad J, Andrews PL. The relationship between gastric motility and nausea: gastric prokinetic agents as treatments. Eur J Pharmacol 2013; 715: 10-14.
9) Ianiro G, Pizzoferrato M, Franceschi F, Tarullo A, Luisi T, Gasbarrini G. Effect of an extra-virgin olive oil enriched with probiotics or antioxidants on functional dyspepsia: a pilot study. Eur Rev Med Pharmacol Sci 2013; 17: 2085-2090.
10) Sacco R, Pucci L, Sivozhelezov V, Pellegrini L, Giacomelli L, Longo V. Prevention of vascular damage with Lisosan G wheat extract: the in vitro basis for a clinical investigation. Eur Rev Med Pharmacol Sci 2015; 19: 1517-1519.
11) Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. Eur Rev Med Pharmacol Sci 2015; 19: 1338-1344.
12) Giacomelli L, Appendino G, Franceschi F, Togni S, Pace R. Omne Ignotum pro Magnifico: characterization of commercial Bilberry extracts to fight adulteration. Eur Rev Med Pharmacol Sci 2014; 18: 3948-3953.
13) Ledda A, Bottari A, Luzzi R, Belcaro G, Hu S, Dugall M, Hosoi M, Ippolito E, Corsi M, Gizzi G, Morazzoni P, Riva A, Giacomelli L, Togni S. Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study. Eur Rev Med Pharmacol Sci 2015; 19: 77-80.
14) Muresan C, Surdea Blaga T, Muresan L, Dumitrascu DL. Abdominal ultrasound for the evaluation of gastric emptying revisited. J Gastrointestin Liver Dis 2015; 24: 329-338.