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Functional dyspepsia investigation for gut abnormalities and evaluation of efficacy, safety & time-bound control study with a proprietary blend consisting of clinically proven synergistic poly-botanical extract & *Bifidobacterium* Infantis (DIGEST study)

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Abstract
Background: To evaluate the efficacy, safety, and quality of life with a proprietary blend of Herbagut & *Bifidobacterium longum* in patients with functional dyspepsia and recurrent gut abnormalities (DIGEST study).
Methods: In a current Post-marketing Phase IV study, 131 patients with functional dyspepsia were included. All the patients were treated with a proprietary blend consisting of Herbagut & *Bifidobacterium longum* (Digespur ®, Nutragenix Healthcare Ltd.) twice daily for 28 days. The efficacy of proprietary blend was assessed by evaluating the changes in epigastric pain, early satiety, acidic regurgitation/heartburn, loss of appetite, and retrosternal discomfort.
Results: All participants completed the 28-day trial, with no adverse events reported during the study. During the study, treatment with marketed preparation demonstrated significant ($p<0.05$) improvement in symptoms such as epigastric pain, regurgitation, retrosternal discomfort, sickness, and loss of appetite from the baseline. Furthermore, the proprietary blend also showed improvement in early satiety, nausea and vomiting in functional dyspepsia patients.
Conclusion: Treatment with a proprietary blend (Digespur ®) for 28 days showed improvement in several gastrointestinal symptoms and overall quality of life. More research with larger sample sizes and diverse clinical and cultural populations is needed.

Keywords: Herbagut, *Bifidobacterium longum*, functional dyspepsia, satiety, heartburn, etc

Introduction
Functional dyspepsia is a complex multifactorial condition that affects populations around the globe and is believed to originate as a gastro-duodenal region. The overall prevalence of functional dyspepsia is estimated to be 16%, subject to variation based on the country and criteria used to establish the diagnosis. A higher prevalence i.e. 10% - 40% is encountered in Western countries and around 5% - 30% in Asian countries [1]. Characteristic symptoms of functional dyspepsia include epigastric pain, epigastric burning, postprandial fullness, or early satiety. Female sex, smoking, acute gastroenteritis, *Helicobacter pylori* infection, non-steroidal anti-inflammatory drug use, and comorbid psychological illness are risk factors for functional dyspepsia. It is generally diagnosed based on the Rome IV criteria. Despite extensive research, the pathophysiological mechanisms underlying functional dyspepsia are complex and poorly explored.
Nevertheless, a few mechanisms associated with developing functional dyspepsia are altered gastric motility, altered visceral sensation, psychosocial factors and genetics [2, 3]. Being a chronic gastrointestinal tract disorder, complete remission from functional dyspepsia is a crucial challenge within the healthcare system. It has far-reaching implications on the patient's quality of life and social functioning. Current treatment for functional dyspepsia includes the eradication of Helicobacter pylori infection, prokinetic agents, proton pump inhibitors, H2 receptor antagonists and central neuromodulators [4].
Diet can be a triggering factor and may account for the varied clinical presentation of functional dyspepsia. Considerable heterogeneity in medical literature limits the use of dietary manipulations as a strategy to minimize symptoms among this patient cohort [5].

As the exact cause of functional dyspepsia is unclear, there is no definitive treatment that can eliminate functional dyspepsia. Emerging evidence accommodates gut microbiota's importance in alleviating symptoms [6]. Different novel formulations have been tested for tolerability and effectiveness in improving gastrointestinal (GI) symptoms [7]. A multi-treatment approach is required for the effective treatment of functional dyspepsia symptoms. Therefore, it is vital to pursue convincing evidence and identify dietary ingredients that could be a valuable asset in treating functional dyspepsia.

Proprietary blend i.e. Digespur® is a combination of Herbagut (400 mg) & *Bifidobacterium longum* subspecies Infantis (1 billion CFU). Herbagut® brings together the power of 14 different herbs to improve overall digestive health and immunity. It contains clinically proven nutraceuticals which helps to keep the gut healthy by maintaining the integrity of its internal lining. Specific pharmacological actions of the herbal ingredients are significantly effective when combined with other plants and are not evident when used alone. Scientific studies on Arjuna have revealed that these plants of varying potency produce a more significant result when combined than in their individual use. The action of the Herbagut® helps to control multi-level gastrointestinal (GI) dysfunction such as irregular bowel habits, GERD, constipation, diarrhea, bloating and related ill-health. It has been proposed that the constituents of Herbagut possess different anti-inflammatory, anti-microbial properties. It also helps protect gut mucosa, modulates gut mobility, improves bowel movement, reduces strains during the evacuation, and improves overall bowel health and well-being [8, 9]. Furthermore, it is reported that the intervention of probiotics improves the gut microbiota and has an effective protective effect on the immune health of the host. A combination of Herbagut & probiotics has not been evaluated in the clinical trial for their efficacy and safety in functional dyspepsia

In the current investigation, a post-marketing surveillance study was conducted to evaluate the proprietary blend containing herbagut 400 mg (Consist of mixture of *Murraya Koenigii*, *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Hemidesmus indicus*, *Cassia fistula*, *Piper longum Linn*, *Cyperus rotundus*, *Boerhaavia diffusa*, *Alpinia galanga*, *Terminalia chebula Retz*, *Centella Asiatica*, *Curcuma longa*, *Andrographis paniculata*, *Zingiber officinale*) and *B. Infantis* 1 billion CFU for its safety and efficacy in individuals with functional dyspepsia. Our study's specific objective was to assess nutraceutical formulation's effect on GI symptom reduction and associated improvement in quality of life.

Methods and Materials

Ethics statement

Ethical approval for the conduct of the study was obtained from the independent ethics committee. Written informed consent was obtained from each patient before performing any study-related procedures (i.e., physical examination, laboratory screening or any other investigational procedure) and before administration of any study-related medication.

Study design and participants

Study design

The study was conducted as a post-marketing surveillance intervention study (Post-marketing Phase IV) in accordance with Good Clinical Practice principles. A total of 131 patients were recruited and the intervention was done for four weeks (one and a half months). The participants were recruited for one month and asked for three visits to the study center – visit 1 (screening and treatment initiation), visit 2 and visit 3. Data analysis was done one month after the completion of the study. During the study period, the participants were advised to use the proprietary blend as prescribed and its effect on GI symptom relief was assessed.

Participants

The study included patients above 18 years of age with a diagnosed functional dyspepsia based on Rome III criteria, who experienced moderate or severe gastro-intestinal symptoms in past two weeks and without structural lesions in the upper gastro-intestinal tract.

Participants who were excluded from the study were patients with a history of dyspepsia not related to functional dyspepsia, history of certain conditions such as gastro-intestinal surgery, malignancy etc., patients with existing disorders such as psychiatric disorders, advanced kidney disease, liver cirrhosis, hypertension, diabetes etc. Patients consuming medication such as prokinetics, erythromycin, acid release inhibitors (histamine 2 receptor antagonists, proton pump inhibitors, or potassium-competitive acid blockers), gastric mucosa protectors, fundal relaxants (sumatriptan, buspirone), cholinergic, anticholinergics, antispasmodics, antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors), aspirin over 100 mg/day, systemic nonsteroidal anti-inflammatory drugs, and systemic glucocorticosteroids were excluded from the study.

Intervention

Each proprietary blend capsule consists of a combination of Herabgut (Consist of mixture of *Murraya Koenigii*, *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Hemidesmus indicus*, *Cassia fistula*, *Piper longum Linn*, *Cyperus rotundus*, *Boerhaavia diffusa*, *Alpinia galanga*, *Terminalia chebula Retz*, *Centella Asiatica*, *Curcuma longa*, *Andrographis paniculata*, *Zingiber officinale*) & *B. Infantis* 1 Billion CFU.

All the patients were instructed to consume one capsule twice a day after food with water for 28 days.

Outcome measures

Gastro-intestinal symptom score

Gastro-intestinal symptom score was assessed on Day 0 (visit 1), 14 (visit 2) and Day 28 (visit 3). Symptoms or parameters evaluated during the study were: epigastric pain/upper abdominal pain, early satiety, nausea, vomiting, acidic regurgitation/heartburn, sickness, loss of appetite, and retrosternal discomfort. At baseline, participants were assessed regarding the problems with these symptoms over the last two months & responses were recorded as follows: 1 - not at all, 2 - less than once a month, 3 - between once a month and once a week, 4 - between once a week and once a day and 5 - once a day or more.

Statistical analysis

Analysis was performed using SPSS software and statistical significance was set at $p<0.05$. In this post-marketing study, the efficacy of study-related medication was analyzed using the 'Intention to Treat' analysis. The demographic details of the patients were analyzed using descriptive statistics. The

difference in clinical response before and after the treatment was assessed using the Kolmogorov-Smirnov test.

Results

Baseline Demographics

A total of 131 participants were recruited during the study and most of the participants were males (62.60%) with a mean age of >60 years (31.3%) (figure 1). All the participants completing the study reported no bothersome side effects during the study period. Among the patients, more than half were already on concomitant medications (64%).

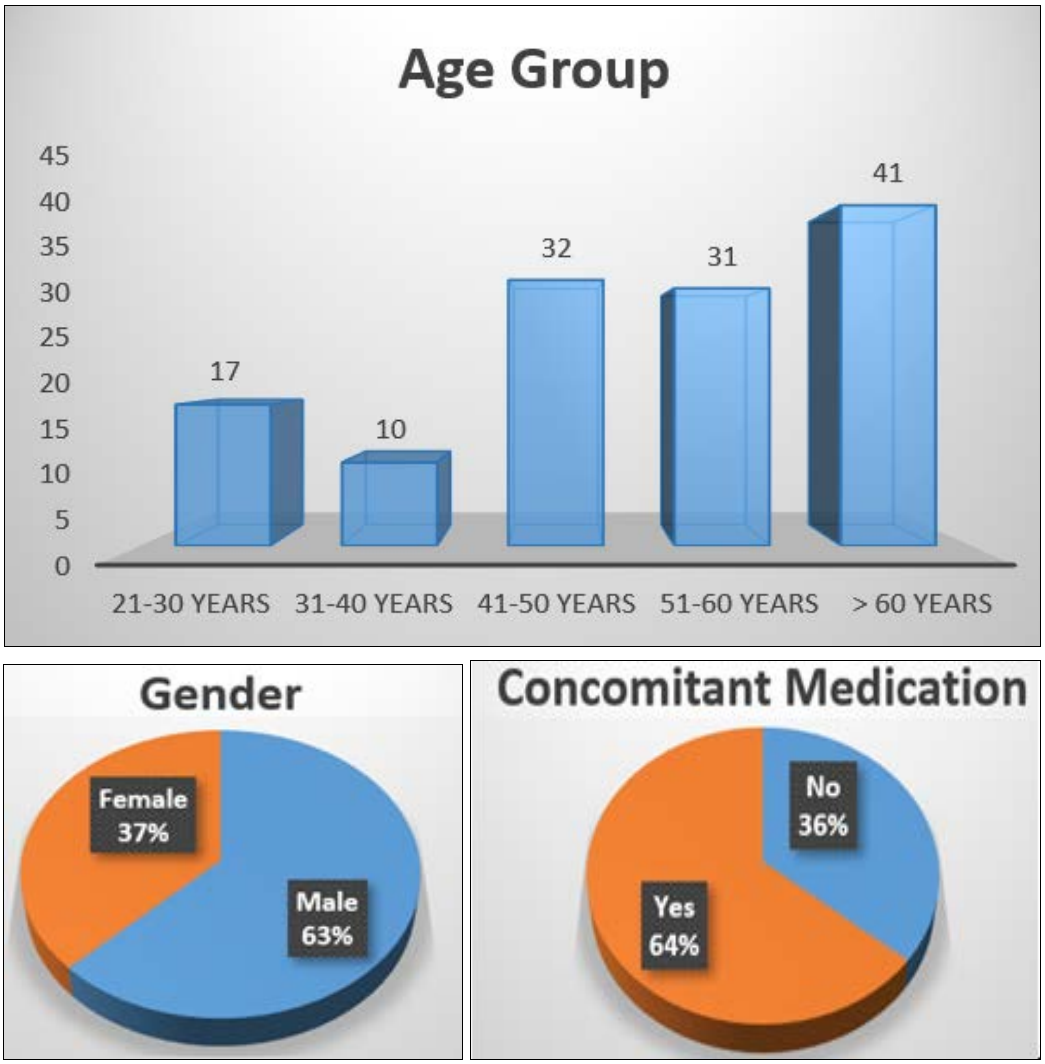

Fig 1: Demographics of the population participated in the study.

Assessment of the efficacy of Digespur ® using different parameters

After 28 days of treatment with a proprietary blend, improvement in different GI parameters of functional dyspepsia was observed (Figure 2). The treatment found to be significantly effective ($p<0.05$) in reducing the epigastric pain from 3.56±0.10 to 2.03±0.11. Early satiety and nausea symptoms were reduced from 3.44±0.11 to 1.94±0.11 and 3.47±0.11 to 1.95±0.11 respectively. The changes observed at the end of the study from the baseline were significant ($p<0.05$). Furthermore, treatment with proprietary blend shows reduction in vomiting and sickness from 3.21±0.11 to 1.86±0.11 and 3.11±0.12 to 1.77±0.10 respectively. The reduction in the symptoms of vomiting and sickness was significant ($p<0.05$) compared to their respective baseline values.

After 28 days treatment with proprietary blend, regurgitation and retrosternal discomfort reduced significantly ($p<0.05$) in patient from 3.48±0.10 to 1.83±0.10 and 3.10±0.13 to 1.75±0.11 respectively. The loss of appetite associated with functional dyspepsia was reduced significantly ($p<0.05$) from 3.15±0.13 to 1.95±0.12 at the end of the treatment (figure 2).

(a) (b)

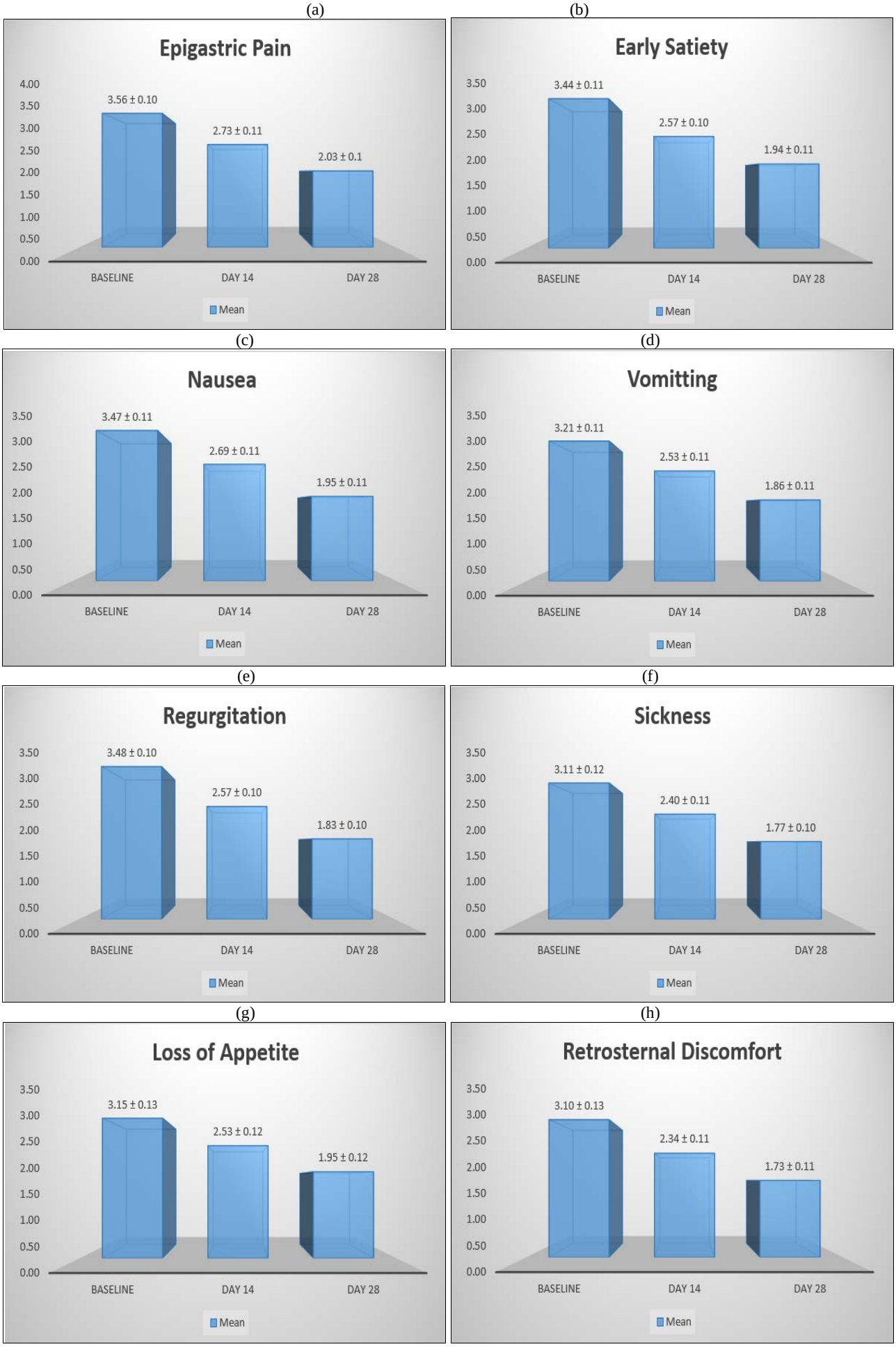

Fig 2: Improvement in the GI symptoms after Digespur ® treatment

Discussion

Functional (non-ulcer) dyspepsia is a common condition. Unfortunately, there is no cure for the vast majority of patients, and available treatments only help a subset of them. The findings of the current postmarketing study using a proprietary blend in patients with functional dyspepsia demonstrated the efficacy of the proprietary blend (Digespur ®) tested for dyspepsia relief. Interestingly, there was no evidence of a reduction in effectiveness over a 4-week treatment period, and further prolonged Digespur ® treatment can show improved response to treatment.

In our study, the proprietary blend has shown significant improvement in the dyspepsia-associated GI symptoms. Treatment was also found to be significantly ($p<0.05$) efficient in improving epigastric pain, early satiety, nausea, vomiting, regurgitation, sickness, loss of appetite & retrosternal discomfort in functional dyspepsia patients. The combination of herbagut & probiotic present in the proprietary blend exhibited enhancement in baseline gastrointestinal parameters after 28 days of treatment.

Similarly, a study by Kalman *et al*. found that probiotics can have a subtle yet effective role in improving distressing GI symptoms such as abdominal pain and distention in the postprandial period. Although this study was conducted using *B. coagulans* based probiotics, it sheds light on their effectiveness in GI symptom reduction [10].

The clinical importance of probiotics in reducing the frequency of GI symptoms such as constipation, flatulence and irregular bowel movements was also previously elaborated by Waller *et al*., using *B. lactis* HN019 strain-based probiotics [11]. The present investigation also shows the reduction in GI symptoms over a 28-day period using a single-strain probiotic. Numerous studies have agreed on the effectiveness of a single-strain probiotic over a multi-strain probiotic for GI diseases [12].

Several mechanisms are involved in the efficacy of a proprietary blend as it comprises different individual ingredients. Such as Turmeric (Curcuma longa) has been shown to improve gastrointestinal function [13], reduce intestinal inflammation [14], and alter the gut microbiome [15]. Zingiber officinale (Ginger) has antibacterial, anti-nausea, and motility-enhancing properties [16, 17], whereas Piper longum has antimicrobial and gastroprotective properties [18]. Furthermore, *Tinospora cordifolia* contains the digestive enzymes amylase, maltase, and isomaltase [19], and was found to be effective as an anti-ulcer agent in rats [20]. Murraya koeniggii [21] and Swertia chirata [22] also has antimicrobial and antibacterial properties *in vitro*. Many of these ingredients have anti-inflammatory properties, and there is evidence that polyphenols have prebiotic-like activities on microbiota [23], which may contribute to the proprietary blend's encouraging GI effects.

The randomized clinical trial conducted by Suzuki *et al* 2013, shows that the dyspeptic relief rate of lansoprazole was 30.4% compared to placebo (6%) after 4-week treatment [24]. On a similar line, the proprietary blend also showed similar results after 28 days of treatment. The use of a proprietary blend for more than four weeks can produce more improvement in a patient with functional dyspepsia.

Conclusion

In conclusion, the post-marketing surveillance study demonstrated a highly significant and clinically relevant efficacy of proprietary blend (Digespur®) in patients with functional dyspepsia after 4 weeks. Furthermore, treatment with a proprietary blend (Herbagut & Bifidobacterium longum) for an extended period, i.e. more than four weeks, can significantly improve patients with functional dyspepsia. More research is required to evaluate the action of a proprietary blend (Herbagut & *Bifidobacterium longum*) in large populations and for an extended period of time.

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Conflict of Interest

Not available

Financial Support

Not available

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