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Role of a novel nutraceutical composition for irritable bowel syndrome management: symptoms relief and unexpected triglycerides-lowering effect

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort and an irregular bowel habit. The prevalence is up to 20% in Western adults, which makes IBS the most common diagnosis in gastroenterology. Despite extensive interest and investigation, IBS's precise aetiology and pathophysiology are poorly understood. Current knowledge suggests that an altered gut microbiota, altered motility, visceral hyperalgesia, and dysregulation of the brain-gut axis are central to IBS. This is also significantly related to a higher prevalence of metabolic syndrome and elevated triglycerides among the adult population. This retrospective study examines the effect of a novel nutraceutical compound, Triobiotix, on gastrointestinal symptoms in IBS patients. Effects on lipid profiles have also been recorded.

Objectives: The focus of this study is to evaluate the effectiveness of Triobiotix, a nutraceutical compound composed of prebiotics and probiotics.

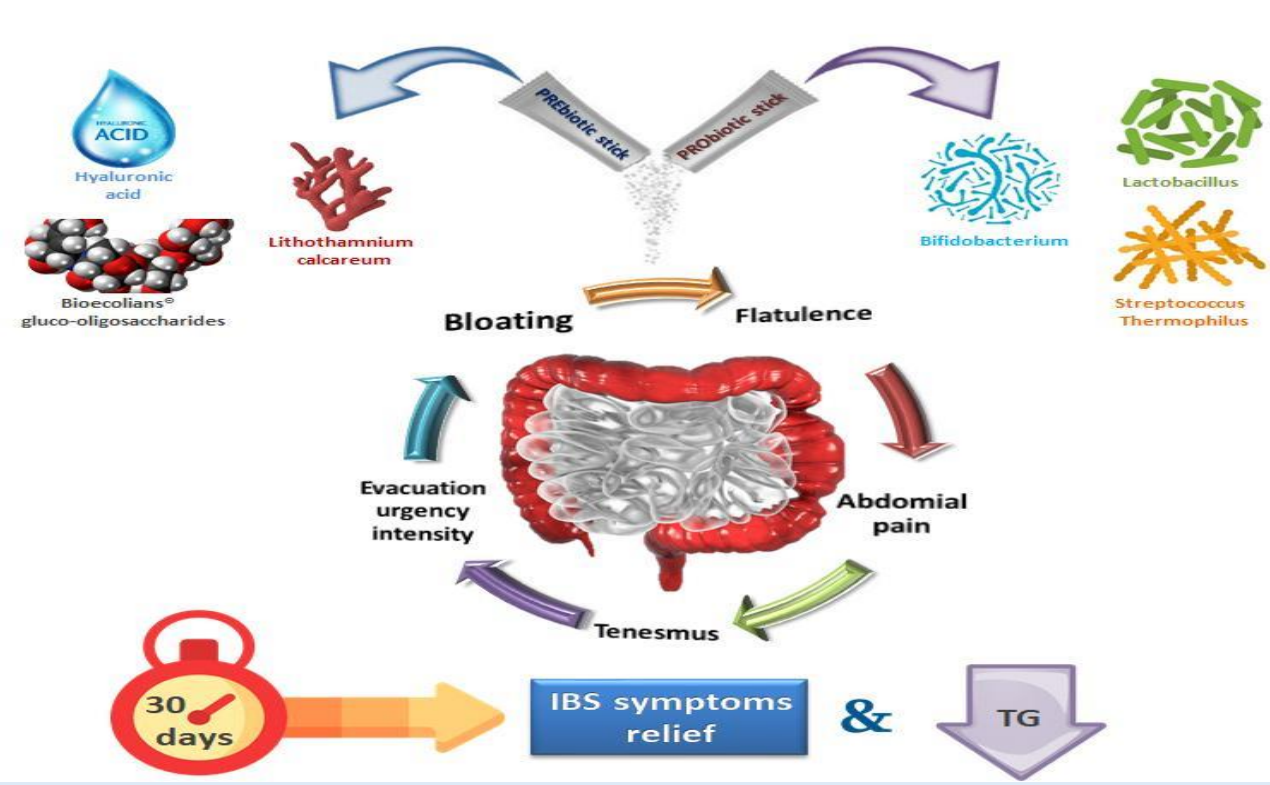
Methods: Triobiotix is a nutraceutical consisting of Maltodextrin; mineralized extract of Lithothamnion (Lithothamnion calcareum (Pallas) Areschoug, thallus dry extract); Bioecolians® gluco-oligosaccharides; Ferment mix (corn starch,

Bifidobacterium animalis ssp. Lactis BLC1 (DSM 17741), Lactobacillus acidophilus LA3 (DSM 17742), Lactobacillus rhamnosus IMC 501 (DSM 16104), Lactobacillus paracasei Streptococcus 501 IMC102 SP4 (DSM 19385); short-chain fructo-oligosaccharides powder. The database of 40 Italian General Practitioners (GPs) was analyzed. A total of 587 patients with IBS treated with Triobiotix were identified. Among them, 535/587 (91.1%) completed the first (T0) and second (T1) visits and their data were available. The primary endpoint of this analysis was to assess if Triobiotix, at a dosage of 1 sachet per day for 30 days, could reduce abdominal pain and bloating, thus resulting in a lower intensity of the main gastrointestinal symptoms. Secondary endpoints were to evaluate presence of any significant changes in triglycerides blood levels and glycaemia.

Results: Treatment with this nutraceutical for one month resulted in a reduction in the frequency and intensity of bloating, abdominal pain, flatulence, and tenesmus. In the 85 patients who reported evacuative urgency, the frequency of the episodes didn't significantly change while their intensity was statistically reduced. Unexpectedly, triglyceride levels also significantly decreased.

Conclusions: Our analysis demonstrates this formulation is effective in the relief of the main symptoms associated with IBS. Moreover, an unexpected effect of this combination of micronutrients on tryglicerides, beyond IBS symptoms, was also found. However, further studies are needed to confirm this evidence and to evaluate the particular compound responsible of this effect.

Keywords: Irritable bowel disease; Triglyceridemia; Nutraceuticals



INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic and recurrent disturbance of the gastrointestinal system functions affecting the colon and small intestine. It is characterized by recurrent abdominal pain associated with ≥ 2 of the following: defecation, a change in stool frequency, and a change in stool form [1]. These symptoms can have a psychological impact, leading to higher levels of depression and anxiety compared to healthy controls [2-4]. IBS affects up to 12% of the European population [5], mainly women under 50 years of age.

The pathogenesis of IBS is multifactorial and heterogeneous [2, 6]. Different mechanisms have been proposed such as alterations in motility, visceral sensation, microbiome, brain–gut interactions, mucosal immune function, bile acid metabolism [2]. Alteration in the normal intestinal flora, or dysbiosis, is considered the primum movens of the syndrome as it modulates intestinal permeability, inflammation, gut motility, and likely quality of life [7].

IBS patients with visceral and somatic hyper-sensitivity have increased intestinal membrane perme-ability [8]. The disruption of the intestinal barrier can lead to local gastrointestinal dysfunction and symptoms [9]. Furthermore, Low-grade inflammation, both local and systemic, was found in IBS patients [2]. This is due to an increased lymphocyte activation and release of proinflammatory cytokines in the bowel [10].

Dietary short-chain carbohydrates and fat also play an important role in IBS [11, 12]. These food components are poorly absorbed in the small intestine and important triggers of functional gut symptoms, by inducing luminal distension via a combination of osmotic effects and gas production [13, 14]. In contrary, elevated levels of poly-unsaturated fatty acids (PUFAs) have been associated as pro-inflammatory[15, 16]. Since the intake of short-chain carbohydrates and the presence of omega-6 and omega-3 PUFAs in humans is ensured by food sources, the central role of one's diet in symptoms control and balancing the pro and anti-inflammatory processes is evident [17].

As discussed, IBS is independently related to a higher prevalence of metabolic syndrome (MS) and elevated triglycerides (TG) [18]. The relationships between IBS and the digestion and absorption of fats have been investigated in other clinical studies [19-21].

To date, an effective IBS treatment is lacking, mainly due to the multifactorial nature of the disorder. Since microbiota alterations have been considered to play a pivotal role in IBS [7, 22, 23], the use of prebiotics and probiotics appears an alternative therapy [24].

The primary endpoint of this study was to to evaluate the effect of a novel nutraceutical composition, Triobiotix, on the symptoms and quality of life of IBS patients, analyzing the database of the participating family practitioners (FPs).

Secondary endpoints were to assess any changes in the perception of well-being reported both patients and doctor, as well as any modifications in lipid profile.

METHODS

Study design and patients selection: The database of 40 family practitioners have been evaluated between January 2022 and September 2022. The study complies with the principle of Good Clinical Practice and the Declaration of Helsinki. Institutional Review Board/Ethics Committee approval is not required for retrospective analysis of database in Italy. Informed consent was obtained from all subjects involved in the study.

Each family practitioner took care of up to 1500 patients and used software that collected several

patient's data (risk factors, diseases, drugs). The following filter criteria has been applied:

- Age ≥18 years old treated with index nutra-ceutical
- IBS diagnosis according to the Rome IV criteria [25]
- Any lipid-lowering nutraceutical or drug
- IBS nutraceutical supplementation
- Following basic recommendations for healthy lifestyle (as reported in table 1)
- Availability of a blood test at time zero and 30-day

Exclusion criteria were defined as follows:

- Low-grade fever, increased levels of C-reactvive protein (CRP) / erythrocyte sedimentation rate (ESR), anemia, thyroid alterations not in stable treatment
- Discontinuous or chronic use of steroids and NSAIDs
- Psychic disorders of clinical relevance even if in treatment
- Eating disorders such as binge eating or anorexia
- Low Body mass Index (BMI< 18.5)
- Diabetes
- Pregnancy

The analysis of the database identified 6,123 IBS patients. among them, 5,982 were on treatment with several nutraceutical supplementations, with 587 being treated with Triobiotix. Because of the nature of this analysis, it has been difficult to select a true comparison group, thus we have analyzed this cohort of patients before and after treatment [26]. From the total number of selected patients, 535/587 (91.1%) IBS patients on treatment with Triobiotrix completed the first (T0) and second (T1) visits and their data were analyzed. Figure 1 showed the selection of the study population.

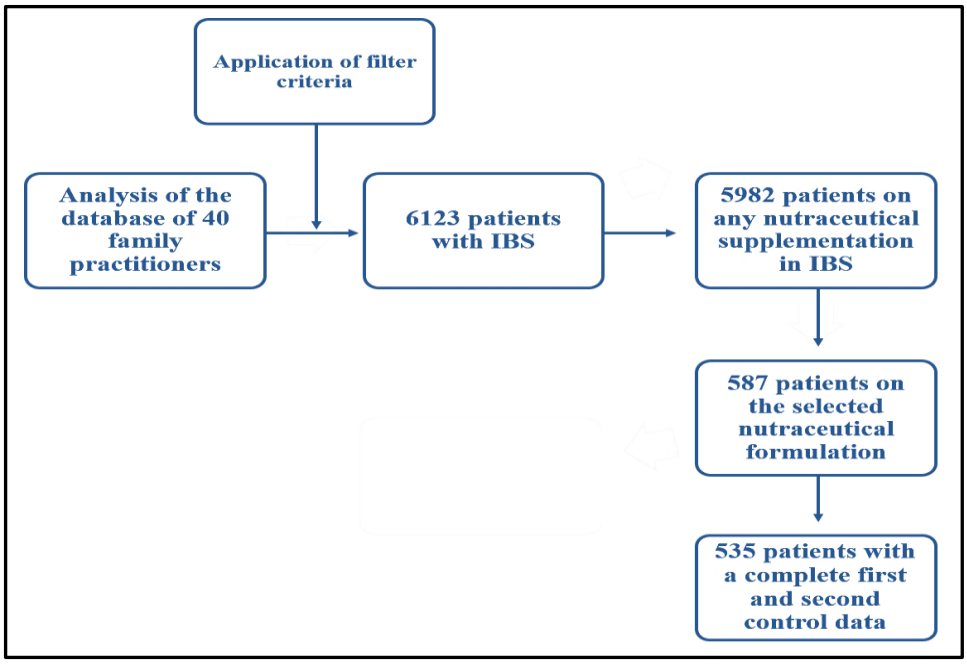


Figure 1. review of approved patients analyzed by practitioners for the use of nutraceutical formulation.

For all included IBS patients, the database reported family and medical history. This included a physical examination (with blood pressure, heart rate and BMI assessment) and laboratory tests-including total

cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

The analysis was only on patients with a sample blood test performed at baseline (T0), before starting the dietary supplement, and at 30-days of follow-up (T1). As for standard practice, recommendations of at least 12 hours of fasting was given to each patient for lipid profile evaluation and the direct measurement of LDL-C was suggested.

Evaluation of symptoms (intensity and frequency) and quality of life (based on all symptoms perceived) were the primary assessment of this analysis. Severity of each IBS case at T0 and T1 was assessed by the IBS Severity Scoring System (IBS-SSS) [27, 28]. This widely accepted scoring system considers the following variables: the intensity of the current abdominal pain and its frequency measured by a visual analogue scale (VAS) 0-100, current abdominal distension expressed through the VAS, satisfaction of intestinal habits through VAS, and degree of interference of the IBS pathology in the patients' work and normal social activities through VAS. The sum of the individual VAS scores allowed IBS patients to be classified into three severity groups: mild (75 to 175), moderate (175 to 300) and severe (> 300).

Frequency (scored from 0 = never, to 3 = always) and intensity (scored from 0=absent, to 3=severe) of several gastrointestinal symptoms such as bloating, abdominal pain, flatulence, urgency, and tenesmus were evaluated at T0 and T1.

Nutraceutical Composition and Usage of Triobiotix®: This nutracenutical is a formula in two sticks: PREbiotic stick pack that contains Maltodextrin; mineralized extract of Lithothamnion (Lithothamnion calcareum (Pallas) Areschoug, thallus dry extract); Bioecolians® gluco-oligosaccharides; flavorings; anti-caking agent: silicon dioxide; sodium hyaluronate (hyaluronic acid); sweetener (sucralose) and PRObiotic stick pack with Ferment mix (corn starch), Bifidobacterium animalis ssp. Lactis BLC1 (DSM 17741), Lactobacillus acidophilus LA3 (DSM 17742), Lactobacillus rhamnosus IMC 501 (DSM 16104), Lactobacillus paracasei, Streptococcusthermophilus 501 IMC102 SP4 (DSM 19385); short-chain fructo-oligosaccharides powder; hydrolyzed corn dextrin; anti-caking agent: silicon dioxide.

This formulation is enriched with Hyaluronic Acid [29] and mineralized seaweed extract Lithothamnion Calcareum, a source of calcium[30] to contribute to the normal function of digestive enzymes.

The innovative T_win packaging technology preserves the vitality of the mixture of 5 different bacterial strains of lactic ferments, selected and mixed to maximize the functionality of the product.

Triobiotix® was given in the form of 1 sachet per day on an empty stomach, for one month associated to Healthy Eating Guidelines (Appendix 1) for at least 30 days. It is a standard practice from the family practitioner to do a weekly follow-up (in medical office or by phone contact) to monitor control subjects and the patients' adherence to recommendations, as well as to evaluate the possible side effects.

Statistical analysis: This is an observational study, thus a formal calculation of the study sample size is not applicable. A descriptive analysis has been performed. Distribution of continuous data was tested with the Kolmogorov–Smirnov and the Shapiro–Wilk test. Normally distributed variables are expressed as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median and interquartile range (IQR). Comparisons between categorical data such as severity scores for irritable bowel syndrome were performed using the $\chi 2$ test. Differences in TC, LDL-C, HDL-C, TG, glicemia during follow-up (T0 vs. T1) were compared using paired t-test due to the normal distribution of the data. For all tests, a p value < 0.05 was

considered statistically significant. All statistical analyses were performed using SPSS Version 27.0. P-values <0.05 (two-tailed) were considered significant.

RESULTS

After filter criteria application, 587 Caucasian patients with IBS were finally identified on novel nutraceutical supplemantation with 535 of them having both T0 and T1 evaluation. Thus, this population represents the final cohort for statistical analyses. Clinical characteristics of the analyzed cohort are described in Table 1. The most frequent IBS sub-type is IBS with constipation (IBS-C), seen more frequently among women.

Table 1: Characteristics of the patients before the use of Triobiotix: T(0).

	N.	Age (years±SD)	IBS with constipation N.	IBS with diarrhea N.	IBS mixed N.
Women	293	51,62±16,430	127	75	91
Men	242	51,19±17,232	95	66	81
Total	535	51,43±16,783	222	141	172

Effects on Symptoms: Treatment with the nutraceutic for one month resulted in a reduction in the frequency and intensity of bloating, abdominal pain, flatulence, and tenesmus. In the 85 patients who reported evacuative urgency, the frequency of the episodes didn't significantly change (p = 0.07) while their intensity was statistically reduced (p = 0.001) as reported in Table 2.

Table 2: Mean data of intensity (0 absent, 1 mild, 2 moderate, 3 severe) and frequency ((0 = never, 1 = rarely, 2 = often, 3 = always) of the symptoms at the first control (T0) and after one month of therapy (T1).

Symptoms	Control T0	Control T1	
	n. 535	n. 535	*P value*
Bloating			
Frequency	1.98 ± 0.81	1.52± 0.91	**0.01**
Intensity	1.49 ± 1.11	1.24±0.96	**0.01**
Abdominal Pain			
Frequency	1.92 ± 0.70	1.36 ± 0.66	**0.01**
Intensity	1.87± 0.671	1.32 ± 0.67	**0.01**
Flatulence			
Frequency	1.92 ± 0.78	1.45 ± 0.78	**0.01**
Intensity	1.39 ± 0.94	0.93 ± 0.90	**0.01**
Evacuative urgency (85 pts)			
Frequency	0.46 ± 0.75	0.50 ± 0.79	0.07
Intensity	0.44 ± 0.91	0.27± 0.65	**0.001**
Tenesmus			
Frequency	1.98 ± 0.82	1.18 ± 0.92	**0.001**
Intensity	1.98 ± 0.82	1.18 ± 0.91	**0.001**

Figure 2 showed the prevalence of IBS patients who referred absent, mild, moderate, and severe gastro-intestinal symptoms's intensitry at T0 and T1.

Mean intensity score of IBS symptoms was significantly lower after 1 month of treatment (1.97±0.82 at T0 versus 1.27±0.89 at T1,p = 0.001). In the 17% of IBS patients the intensity of the symptoms was reported absent at the T1 control.

The effect of symptoms reduction after treatment is evident in all degrees of severity, but it is remarkable that more than half of patients who initially experienced severe symptoms reported a reduction in the intensity after treatment.

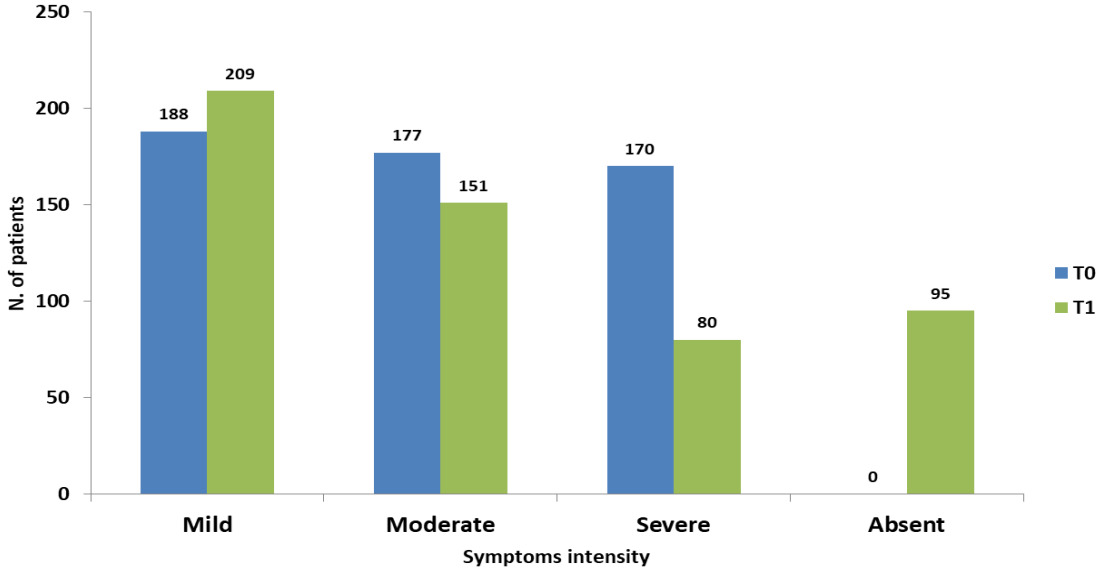


Figure 2: Frequency and Intensity of symptoms in IBS Patients. Values T0 and T1 compared.

Wellness assessment: The patients, both at T0 and at T1 control, expressed their perception of wellness on a Likert scale from 0 to 10 (0: very bad; 10: very well). The doctors did the same, regarding the patient's general condition. These data, which demonstrate a significant and positive difference in the perception of well-being after treatment with nutraceutical formulation, are summarized in Table 3.

Table 3: Perception of well-being after treatment of IBS patients.

Assessment of general well-being with respect to the IBS	Control T0	Control T1	*P value*
Wellness as perceived by the patient (0-10)	4.23± 3.11	4.95± 3.20	**0.001**
Wellness as assessed by the doctor (0-10)	4.24± 3.04	4.96± 3.13	**0.001**

Effects on metabolic profile: For this evaluation, we analyzed all of the study population and the second analysis patient with triglyceride levels ≥ 150mg/dL. The lipid profile of the study population is reported in table 4. At the T0 evaluation, total cholesterol values were 208.07±34.9mg/dL, while LDL-cholesterol values were 139.86±37.9mg/dL and Triglycerides averaged 136.37±66.4 mg/dL.

At the T1 control, a nonsignificant decrease in lipid profile was observed with the total cholesterol values 204.91± 43.9(p = 0.15) and LDL-cholesterol 136.22±38.9 (p = 0.12). Triglycerides also decreased (mean values 129.13±67.9 mg/dL) with a major trend to reach statistical significance (p = 0.078).

Although diabetic patients were not included in final analysis, glycaemia values significantly decreased at the T1 control, showing mean values of 93.11 ±14.6mg/dl (p = 0.022), while still being within normal range at T0, 93.31±14.7mg/dl. More interestingly, the analysis of patients with triglyceride levels ≥150mg/dL showed a significant decrease between T0 and T1 for triglyceride values with a Δ of 20mg/dL as reported in table 5. No statistical difference was observed in the other components of the lipid profile.

Table 4: Metabolic profile in the study population.

N .	Control T0 (535)	Control T1 (535)	*P value*
Total Cholesterol (mg/dL)	208.07 ± 34.9	204.61 ± 43.9	0.15
LDL-cholesterol (mg/dL)	139.86 ± 37.9	136.22 ± 38.9	0.12
HDL-cholesterol (mg/dL)	41 ± 7.2	42 ± 9.5	0.052
Triglyceridemia (mg/dL)	136.37±66.4	129.13 ± 67.9	0.078
Glycemia (mg/dL)	96.31± 14.79	93.11 ± 14.66	**0.0022**

Table 5: Metabolic profile in patients with triglyceride levels ≥150mg/dL.

N .	Control T0 (232)	Control T1 (232)	*P value*
Total Cholesterol (mg/dL)	219.16± 24.3	215.97±31.3	0.22
LDL-cholesterol (mg/dL)	145.23±22.8	144.8± 21.2	0.83
HDL-cholesterol (mg/dL)	38±4.8	39±6.2	0.052
Triglyceridemia (mg/dL)	176.28±26.8	155.41±35.92	**<0.0001**

Response to treatment according to the gender: Finally, we analyzed the symptom data in men and women separately since IBS is more frequent in the female. In Table 6 is reported how at the T0 control women report major intensity of severity of symptoms than men, expecially for meteorism. However, the response to treatment was similar in both sexes with the only exception of the reported pain intensity, which was significantly decreased in women and bloating intensity that was significantly reduced in men. The assessment of the severity of IBS symptoms, was indeed not significantly different according to the gender.

Table 6: Response to treatment according to the gender

	Control T0			Control T1		
	Women (293)	**Men (242)**	***p***	**Women (293)**	**Men (242)**	***p***
Bloating						
Frequency	2.01±0.81	1.98±0.79	0.660	1.33±0.72	1.20± 0.63	0.136
Intensity	1.64±1.08	1.40±1.63	**0.042**	1.26±0.69	1.72±0.65	0.430
Abdominal Pain						
Frequency	1.97±0.72	1.92±0.73	0.381	1.23±0.83	1.21±0.60	0.739
Intensity	1.70±0.65	1.72±0.65	0.144	0.96±0.91	1.21± 0.87	**0.001**
Flatulence						
Frequency	1.97±0.77	1.61±0.80	0.131	1.91±0.90	0.88±1.04	1.330
Intensity	1.41±099	1.38±0.94	0.75	1.41±0.95	1.41±0.95	0.580
Evacuative urgency (85 pts)						
Frequency	0.46±0.74	0.48±0.75	0.762	0.54±0.77	0.59±0.81	0.573
Intensity	0.44±0.89	0.48±0.89	0.680	0.25±0.65	0.29±0.52	0.666
Tenesmus						
Frequency	1.92± 0.86	1.94±0.84	0.787	1.17± 0.99	1.18±0.88	0.902
intensity	1.86± 0.88	1.98±0.83	0.108	1.19± 0.91	1.18±0.92	0.899
IBS severity	2.03±0.81	1.95±0.72	0.23	1.32±0.91	1.19±0.85	0.091

DISCUSSION

The present analysis, with all the limitations of a retrospective study without a control group, shows administration of this nutraceutical composition in IBS patients without comorbidities, at a dosage of 1 sachet per day for 30 days, is effective in reducing the IBS severity in all 3 variants (constipation, diarrhea, and mix) by:

- reducing bloating, abdominal pain, taking control of frequency and intensity of flatulence, reducing intensity of evacuation urgency, and tenesmus.
- positively modifying the perception of wellness, both reported by the patient and assessed by the doctor
- reducing blood glucose levels and triglycerides levels

These findings might be of clinical relevance in the quick symptoms management in IBS patients. The reduction of symptoms severity as well as the perception of well-being after treatment are good indicators of improved quality of life.

Several studies have reported that IBS is associated with an alteration of the intestinal barrier and gut microbiota [23]. Specifically, an imbalance between the "good" and "bad" bacteria occurs. In patients with IBS, a higher concentration of the bacterium Methanobrevibacter smithii is reported [31]; that is a producer of methane which also acts on intestinal transit and a reduction in Lactobacilli and Bifidobacteria, which promote the integrity of the intestinal epithelium and have an anti-inflammatory action [23]. The present nutraceutical is enriched of Bifidobacteria, Lactobacilli and Streptococcus thermophilus. The 'micro' action of probiotics is able to prevent and repair this damage to the intestinal barrier [32]. Probiotics, by modifying the bacterial flora, can reduce the IBS symptoms [33]. In particular, Lactobacilli and Bifidobacteria's resistance to gastric acids and bile salts may improve the symptoms of the IBS patients. Additionally, their anti-inflammatory

properties will reduce symptoms of irritation both local and systematically [34-37]. Probiotics are used in IBS with diarrhea, but in association with prebiotics (in particular soluble fibers such as psyllium or hydrolysed guar gum), are useful for reducing constipation in forms with prevalent constipation or in mixed forms [24] . These are not toxic to the body and do not have long-term side effects, but generally, cyclic therapies are recommended to rebalance the intestinal bacterial flora [24]. Clinical studies support the use of Bifidobacteria and Lactobacilli in improving the gastrointestinal disturb-ances of IBS [31, 35, 36].

Unlike probiotics, prebiotics are food ingredients, not digested in the initial tract of the human intestine, which stimulate the growth and activity of non-pathogenic microorganisms already present in the intestine itself[24]. Their use in facilitating the action of probiotics is also supported by scientific evidence[24].

The role of “functional foods” in the management of human diseases is now supported by several studies[38-40] and when functional foods are used for prevention and/or curing of any disease/disorders, it becomes a “nutraceutical”[41]. On this regard, functional food science is the new discipline with the primary scope to stimulate a function-driven approach on these foods[40, 42] as reported for some bioactive agents[43]. Japan has been the first country regulating functional food since 1984[44]. Based on the definition from Functional Food Center that defines functional foods as “natural or processed foods that contain biologically-active compounds able to reduce the risk of pathologic processes and improve metabolic and physiologic processes”[40], the composition evaluated in the present study migh be considered a functional food.

It includes both probiotics and prebiotics that are administrated separately to reduce an early interaction before to reach the large intestine, thus leading to bloating. A recent meta-analysis evaluating 15 randomized controlled trials demonstrated that probiotics, such as Bifidobacterium, Lactobacillus and Streptococcus strains, are of clinical utility for reducing functional constipation in adults by increasing stool frequency, intestinal transit time and stool consistency[24]. Specifically, the Lactobacillus acidophilus NCFM reduces intestinal pain and further studies have highlighted itsanalgesic effect by increasingμ-opioid and cannabinoid receptors expression on intestinal epithelial cells [45]. It has been reported that Lactobacillus rhamnosus HN001 has the ability to modulate the gut microbiota composition, leading to a significant reduction of potentially harmful bacteria and an increase of beneficial ones[46]. L paracasei is known for its anti-inflammatory properties and for reducing visceral hypersensitivity[36] while S thermophilus reduces intestinal wall damage[47]. This nutraceutical formulation by using these prebiotics simultaneously,takes advantages from their synergistic action and protective properties thus resulting in clinical benefits as indicated by the patients and the doctors’ perception. Despite the potential benefits observed in this analysis, well-designed interventional studies are needed to better evaluate the specific effect of this nutraceutical in the different types of IBS.

As secondary analysis, we have evaluated the effect on lipid profile and glicemia. Despite diabetic patients we excluded from this evaluation we observed a significant 3 mg/dL reduction in glucose levels in the study population. More interestingly we found also a mean of 20mg/dL reduction in triglyceride levels in 30 days treatment that was of statistical significance despite the mean value of TC, LDL-C and HDL-C did not change significantly. A trend in HDL-C increase was observed. These findings are in line with other previous obervations in this field[18, 48]. It has been postulated that link between high triglyceride levels, metabolic syndrome (MS) and IBS might exist[48, 49]. A previous report study

has already indicated that IBS might be associated with elevated triglyceride levels[18]. Later, in another study from Korea, was reported a higher prevalence of MS in IBS patients than control (32.5% vs.12.7%), with a risk of MS in IBS patients still increased even after adjusting for confounding factors[50]. More recently, a population-based, 5-year follow-up cohort study seems to confirm thatthe risk of IBS was significantly increased in both MS and Pre-MS patients, reinforcing the notion that MS status, especially larger waist circumference and higher triglycerides, may be potential risk factors for IBS [51]. In our analysis we found higher TG levels in IBS patients with a significant reduction after nutraceutical administration. Several mechanisms might be correlated with this positive effect but several evidence seems to indicate that the effects on gut microbioma might be the primary mechanism[7, 23]. Gut microbioma has been identified as new endocrine organ system, influencing lipid metabolism and atherosclerotic disease [52]. It was found in humans that triglycerides were higher and HDL-C were lower in individual with low microbiota diversity [53-54].

Moreover, a cross-validation analysis performed on a cohort study revealed that the gut microbiome contributes to a 6% of variance of serum triglycerides and 4% in HDL-C attributed to the microbiota composition [55]. It has been reported that gut microbiota metabolizes the dietary lipid phosphatidylcholine to trimethyl amine, promoting atherosclerosis and inflammation [56]. Finally, levels of choline, trimethylamine N-oxide and betaine have been linked to cardiovascular diseases development [57]. On this regard, changes in gut metagenome has been associated with the symptomatic atherosclerosis [58]. Selective manipulation of gut microbiota might be a potential therapeutic approach for improving lipid profile, thus further reducing cardiovascular risk.

Limitations: Despite the major findings, this study shows some limitations to be stated: a) the retrospective analysis, b) the lack of a control group c) the sample size that is relatively small, d) the geographical location that is restricted few areas and e) the follow-up that is limited to 30 days, f) a placebo effect cannot be completely rule out. Another potential limitation may be represented by the collection of data from the family practitioners database. Also, adherence to Healthy Eating Guidelines and Triobiotix supple-mentation cannot be verified. Finally, despite the recommendation on the 12 hours fasting before lipid profile measurement, we cannot be certain this was achieved in all participants.

CONCLUSION

This analysis shows this formulation is effective in the relief of the main symptoms associated with IBS. Moreover, an unexpected effect of this combination of micronutrients on tryglicerides, beyond IBS symptoms, was also found. Further studies are needed to confirm this evidence and to evaluate the particular compound responsible of this effect.

Abbreviations: IBS: Irritable Bowel Syndrome, CRP: C-reactvive protein, ESR: erythrocyte sedimentation rate, NSAIDs: Non-steroidal anti-inflammatory drugs, LDL-C: low-density lipoprotein, HDL-C: high-density lipoprotein, TG: trygliceride, TC: Total cholesterol, FPs: family practitioners, BMI: body mass index, VAS: visual analogue scale, IBS-C: Irritable Bowel Syndromewith constipation, MS: metabolic sybdrome, SD: standard deviation, IQR: interquartile range.

Author Contributions: Conceptualization, F.N. and A.Sn.; methodology, A.Sn., A.S. and G.P.; validation, F.N., G.P. and A.S.; formal analysis, R.M., F.N. and S.C. ; investigation, G.P. and A.S.; resources, G.P.; data

curation, F.N.; writing—original draft preparation, F.N.; writing—review and editing, G.C.; visualization, G.G and A.Sn.

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APPENDIX

Table 1. Healthy Eating Guidelines for Irritable Bowel Syndrome (from the Global Resource of Nutrition Practice).

1. Keep a food and symptom journal. This will help you to learn if your GI symptoms are related to your current food habits. • If it becomes clear a specific food or beverage causes you discomfort, try taking it out of your diet to see if this helps. For example, some people may find that spicy foods trigger their symptoms. • If your symptoms don't improve after a few weeks, you can add the food back into your diet. • If you eliminate many foods from your diet, you may be missing some important nutrients. Talk to a registered dietitian about other foods to eat to make sure you are getting all the nutrients you need.
2. Improve your overall digestion • Eat at regular times each day. • Avoid eating late at night. • Enjoy three meals and up to one to two snacks spaced evenly throughout the day. • Try not to overeat at any one time. • Eat when you are relaxed. Give yourself enough time so that you can eat your food slowly. • Limit distractions and try not to eat at your desk or in front of the TV. • Reduce the amount of air you swallow: chew your food well, avoid chewing gum and avoid carbonated beverages.
3. Drink plenty of fluids • Choose water as your main fluid. • Aim for about 1.5-3 L of fluid each day. Keeping well hydrated may help if you have constipation. • If drinking large amounts of fluids with meals causes your symptoms to get worse, try drinking your fluids between meals instead.
4. Aim for a fibre intake that works for you • Some people find that either too much or too little fibre can make their symptoms worse. If you eat a higher fiber diet, try decreasing the amount of fiber and see if your symptoms improve. If you eat a lower fiber diet, try increasing your fiber intake slowly and see if your symptoms improve. • There are two main types of fibre: - Soluble fibre absorbs extra water in the colon and forms a thick gel that softens stool. It may help to relieve both diarrhea and constipation. Oats, oat bran, ground flax seed and psyllium are good sources of soluble fibre. - Insoluble fibre adds bulk to your stool and can help you have regular and pain-free bowel movements. It is found in wheat bran, bran cereals and whole grain products such as whole wheat bread and pasta and brown rice. If you find these foods make your symptoms worse, limit them and eat foods with soluble fibre instead.
5. Avoid high fat foods and snacks • Eating too much fat at one time may cause cramping and diarrhea. Examples of high fat foods include higher fat cheese, whipping cream, ice cream, prime rib and spareribs, regular ground beef, sausages, bacon, chicken with the skin on it, fried foods, pastries, cakes, cookies, and chocolate.

• Eating a moderate amount of healthy dietary fat, such as canola, soy and olive oil, avocado, nuts and seeds, spread throughout the day, is part of a healthy, balanced diet.

• Choose lower fat dairy, such as low-fat yogurt, lean meats and lower fat cooking methods, such as baking instead of pan frying in oil.

6. Adjust your caffeine intake based on your symptoms

• Caffeine stimulates the GI tract which may make diarrhea worse. If you have diarrhea, limit or avoid caffeine.

• Caffeine is found in coffee, tea, colas and some other soft drinks, energy drinks and chocolate.

• Health Canada suggests having no more than 400mg of caffeine per day (the amount found in three small cups of coffee).

7. Limit or avoid alcohol

• Alcohol irritates the stomach and GI tract which may trigger your symptoms. If you choose to drink alcohol, limit yourself to no more than 10 drinks a week for women and no more than 15 drinks a week for men. Have no more than 3 drinks (for women) and 4 drinks (for men) on any single occasion.

• A standard drink is:

- 341 mL (12 oz.) bottle of 5% beer, cider or cooler
- 142 mL (5 oz.) glass of 12.5% wine
- 43 mL (1.5 oz.) shot of 40% spirits

8. Learn more about the Low FODMAP Diet

• If following the advice in this handout does not make your symptoms better, consider speaking with a registered dietitian about the low FODMAP diet.

• FODMAP's are types of carbohydrates that are poorly digested and may cause gas, bloating and pain in people with IBS.

• The aim of this diet is to help you find out which of the FODMAP foods cause you symptoms and in what amounts. The goal is to provide the most flexible and varied pattern of eating that provides the best control of your symptoms.

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