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Clinical Observations on the Effects of a Dietary Supplement (GI Regenerate™) on Patients' Gastrointestinal Symptoms and Quality of Life Assessments

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Abstract

Background: Different treatments have been developed and used to control symptoms and improve quality of life in patients with digestive diseases and disorders. Although the use of drugs or alternative approaches has improved symptom severity in some but not all patients, often these improvements were not sustainable. **Objectives:** An open label clinical study was initiated to determine if oral capsules containing a dietary supplement of herbs and oils (GI Regenerate™) could reduce self-reported gastrointestinal symptoms and improve quality of life (QOL) indicators in patients with gastrointestinal conditions. **Methods:** Participants included 50 patients (40 females and 10 males) of mean age of 51.1 ± 12.7 years (range, 24 - 77 years) with a diagnosis of a gastrointestinal disorder or gastrointestinal symptoms. These patients consumed five soft-gels containing the test supplement 30 minutes before each meal for 90 days. Symptoms were evaluated by medical staff, and patient health status was self-reported using a validated quality of life questionnaire (Quality of Life Digestive Survey) designed for functional digestive disorders. Exit interviews (Patient Global Impression of Change, PGIC) were conducted by the medical staff. **Results:** Participants in the study responded with improved symptom severities and QOL scores to the test dietary supplement within the 90 day period; most improvements occurred within 20 days on the test dietary supplement. By the end of the study there were significant overall global improvements in the symptoms and QOL health surveys ($p = 0.0183$),

with significant improvements in symptom discomfort ($p = 0.0004$), daily activities ($p = 0.029$) and anxiety ($p = 0.018$). In contrast, there were insignificant improvements in diet ($p = 0.398$), sleep ($p = 0.136$), health perception ($p = 0.686$), coping with the disease ($p = 0.309$) and impact of stress ($p = 0.785$). Using the PGIC exit interview that measured each patient's impression of overall global change in symptoms and QOL these data also indicated overall significant improvements in symptoms and in satisfaction with the test supplement (moderately better improvements in symptoms and QOL or score of 4.8 ± 0.169, $p < 0.0001$). There were no significant differences in the responses between males and females, and no significant differences between older (>50 years) versus younger (<50 years) subjects. There were also no safety issues that arose during the trial. **Conclusions:** The GI Regenerate™-natural dietary supplement safely and significantly reduced gastrointestinal symptoms and improved quality of life in subjects with a broad spectrum of gastrointestinal disorders and symptoms.

Keywords

Gastrointestinal Symptoms, Quality of Life, Dietary Supplement, Digestive Disorders, Herbal Remedies, Dietary Oils

1. Introduction

There is a rather large burden to the United States population of morbidity, mortality and cost due to gastrointestinal (GI), liver and pancreatic diseases and disorders [1] [2], and this appears to be true in other nations as well [3]. With its aging population, the United States faces an increasing prevalence of digestive diseases over time [2]. This is likely to result in an overall worsening of the productivity and quality of life (QOL) in the aging population [4] [5].

Different treatments have been developed and used to control symptoms and improve QOL in digestive diseases and disorders [6] [7]. Among the pharmaceutical treatments that are commonly used, such as corticosteroids, aminosalicylates, antibiotics and immunosuppressive drugs, improvements in symptoms have been found, but not in every patient, and often these improvements are not sustainable. Also, the drugs that are often prescribed can have adverse effects in some patients. Thus complementary or alternative medicine approaches have been used to avoid the adverse effects of drug treatments and improve treatment outcomes [6] [7].

Among the alternative medical approaches to the treatment of GI diseases and disorders is the use of herbal combinations, and this has proved beneficial for many patients [8] [9] [10]. There is a rich history that goes back thousands of years of using single and multiple herbal formulations to treat digestive diseases and disorders [8] [10]. In the United States, a large proportion of patients with digestive disorders have tried some form of herbal treatment [10] [11]. The most commonly used herbal treatments for digestive diseases and disorders in the US

have their origin in traditional Chinese medicine [10].

One such combination of herbs and oils that has been used for years in China to treat digestive disorders has been utilized in the current study. This same combination dietary supplement has had different names (GIC, MEBO Gastrointestinal Capsule, Dr. Xu's GI Formula, or more recently GI Regenerate™), and it has been the subject of several scientific and clinical studies in China. These studies include: survival and growth promotion of intestinal and stomach epithelial cells [12] [13], clinical treatment studies on ulcerative colitis [14], gastroesophageal reflux disease [15], gastric ulcers [16], peptic ulcers [17], and repair of gastrointestinal damage due to ethanol [18] or infection [19].

Using a validated QOL questionnaire for functional digestive disorders [20] and patient global impression of change scores (PGIC) taken during exit interviews by contributing physicians this same dietary supplement formulation, or GI Regenerate™, has been examined for its use in treating digestive disorders and symptoms in North American patients.

2. Materials and Methods

2.1. Materials

GI Regenerate™ is a patented natural supplement containing a mixture of herbal ingredients and edible oils. It contains stigmasterol, campesterol, beta-sitosterol, chalinosterol, clionasterol, brassicasterol, alpha-spinasterol, daucosterol, desmosterol, poriferasterol and an edible wax [21]. This base mixture was placed (250 mg each) into soft gel capsules. The natural dietary supplement used in the clinical study was provided by MEBO Life Sciences, Brea, California.

2.2. Methods

An open label, independent Institutional Review Board (IRB)-approved study was initiated using subjects recruited from Southern California with formally diagnosed digestive disorders and diseases, such as ulcerative colitis, gastritis, esophagitis, gastroesophageal reflux disease (GERD), Crohn's disease, irritable bowel syndrome (IBS), or other digestive disorders. The study recruitment was limited to patients attending the Center for New Medicine, Irvine, California who volunteered for the study. The number of subjects was determined by the number of patients who volunteered and could be adequately scheduled, examined and treated by available staff during the trial period of January 2019 to January 2020.

The 40 females and 10 males recruited to the study presented with a variety of signs and symptoms related to digestive disorders (**Table 1**). Exclusionary criteria included subjects who were taking immunosuppressive drugs, or had cognitive impairment, or were pregnant, lactating or below the age of 18 years. Each subject was directed to take 5 capsules of GI Regenerate™ 30 min before meals 3X per day for the 90-day study period. Participants were advised not to change any of their daily medications, diet or routine during the study.

Table 1. Diagnoses/symptoms of subjects in the clinical study.

Diagnosis/Symptom*	*N*
Female Subjects (*Total*)	40
Abdominal bloating	26
Abdominal pain	22
Celiac disease	2
Constipation	25
Crohn's disease	3
Diarrhea	23
Fatigue	14
Flatulence	9
Food allergy	7
Gastric pain	3
Gastritis	10
GERD	17
IBS	16
Intestinal malabsorption	3
Nausea	10
Obesity	1
Regurgitation	4
Ulcerative colitis	7
Male Subjects (*Total*)	10
Abdominal Bloating	2
Abdominal pain	6
Celiac disease	-
Constipation	7
Crohn's disease	1
Diarrhea	9
Esophagitis	1
Fatigue	3
Flatulence	2
Food Allergy	3
Gastric pain	6
Gastritis	-
GERD	6
IBS	1
Intestinal malabsorption	-
Nausea	1
Obesity	1
Regurgitation	1
Ulcerative colitis	1

*Subjects may have more than one diagnosis and have multiple symptoms. IBS, irritable bowel syndrome; GERD, gastroesophageal reflux disease.

Study subjects were monitored at various times using a validated patient questionnaire for functional digestive disorders and QOL (Appendix Figure 1 in reference [20]). The data were normalized to baseline and analyzed as: a) Overall Global Scores; and subsets of data were normalized to baseline and analyzed as: b) Daily Activities Scores, c) Symptom Discomfort Scores, d) Anxiety Scores, e) Diet Scores, f) Sleep Scores, g) Coping with Disease Scores, h) Health Perception Scores, and i) Stress Impact Scores [20].

Subjects were also subjected to exit examination and surveys conducted by professional staff physicians of the Center for New Medicine of Irvine, California. In this (PGIC) analysis participants were asked whether their overall changes in symptom severity and QOL were very much better (score of 6), moderately better (score of 5), a little better (score of 4), no change (score of 3), a little worse (score of 2), moderately worse (score of 1) or very much worse (score of 0) (**Appendix Figure A1** of this paper). The mean satisfaction scores were determined and analyzed statistically.

2.3. Statistical Analysis

For statistical analysis we used generalized estimating equations (GEE) for the regression parameters as introduced by Liang and Zeger as a method for estimation of regression model parameters when dealing with correlated data [22] [23]. Generalized estimating equations (GEE) are a convenient and general approach to the analysis of several kinds of correlated data. The main advantage of GEE resides in the unbiased estimation of population-averaged regression coefficients despite possible misspecification of the correlation structure. Our longitudinal research was aimed at describing the marginal expectations of the outcome as a function of the predictors [24].

The objective of analyses that we have done and performed were to examine: (1) whether the QOL scores differed over the study time points; (2) whether the QOL scores differed over the study time points between males and females; and (3) whether the QOL scores differed over the study time points between age < 50 and age ≥ 50. Data were analyzed with significance defined as $p < 0.05$ and presented as mean data with 95% confidence levels.

The exit survey (PGIC) was conducted with 28 subjects, and satisfaction scores were calculated and analyzed by a one-sided, one sample t-test. In this analysis a significant overall improvement in exit scores would be a composite satisfaction score greater than 3.0. All of the statistical analyses were performed independently by the Statistical Unit of the Division of General Medicine, Department of Medicine, University of California, Irvine.

2.4. Safety Issues

The safety of patients was carefully monitored during the trial. Any issues of adverse reactions to the test supplement were carefully recorded and monitored during the trial. Potential changes in blood chemistry were monitored each

month during the clinical study using the NutrEval™ diagnostic blood evaluation panel (Genova Diagnostics, Asheville, NC). In this panel standard blood chemistry and a panel of blood levels of antioxidants, vitamins, minerals, essential fatty acids, probiotics, pancreatic enzymes, and amino acids were monitored at the beginning and each subsequent month during the trial period.

3. Results

3.1. Participants in the Study

There were 50 participants in the IRB-approved clinical study (40 females, 10 males). They had a mean age of 51.1 ± 12.7 years (range, 24 - 77 years) and presented with a diagnosis of a gastrointestinal disorder. A summary of the participants and their presentation with a variety of digestive disorders and diseases (with multiple gastrointestinal symptoms) is summarized in **Table 1**.

3.2. Quality of Life Determinations

Using the validated digestive disorders questionnaire of Chassany, *et al.* [20] patients were examined for their responses in each survey category every 10 days during the 90-day test period (**Figure 1**). After the 90-day period, the analyzed results of the study indicated that there were significant overall global improvements in the health surveys ($p = 0.0183$) (**Figure 1(a)**), with significant improvements in symptom discomfort ($p = 0.0004$) (**Figure 1(b)**), daily activities ($p = 0.029$) (**Figure 1(c)**) and anxiety ($p = 0.018$) (**Figure 1(d)**). In contrast, there were insignificant improvements in diet ($p = 0.398$) (**Figure 1(e)**), sleep ($p = 0.136$) (**Figure 1(f)**), health perception ($p = 0.686$) (**Figure 1(g)**), coping with the disease ($p = 0.309$) (**Figure 1(h)**) and impact of stress ($p = 0.785$) (**Figure 1(i)**). Most health response improvements over baseline occurred within 20 days from initiating the dietary supplement (**Figures 1(a)-(d)**).

Based on the results from the GEE models, regression parameters indicated that the improvements in overall global symptoms and QOL scores were consistent and occurred with a low degree of variance. The estimated changes from baseline of the eight dimension scores are shown in **Table 2**. The dimension scores included: daily activities (DA), anxiety (AN), diet (DI), sleep (SL), discomfort (DT), health perceptions (HP), coping with disease (CD), and impact of stress (IS). In addition, two overall measures, the estimated change from baseline in the global score (GS) and an alternative scoring of the global score (Alt GS) are also displayed. The Table illustrates the low degree of variance in estimated changes from baseline in dimension scores and global scores over the 10 survey time points.

3.3. Exit Interviews

Exit interviews (PGIC) with each participant were conducted by the clinical study physicians (**Appendix Figure A1**). The exit interviews indicated that the

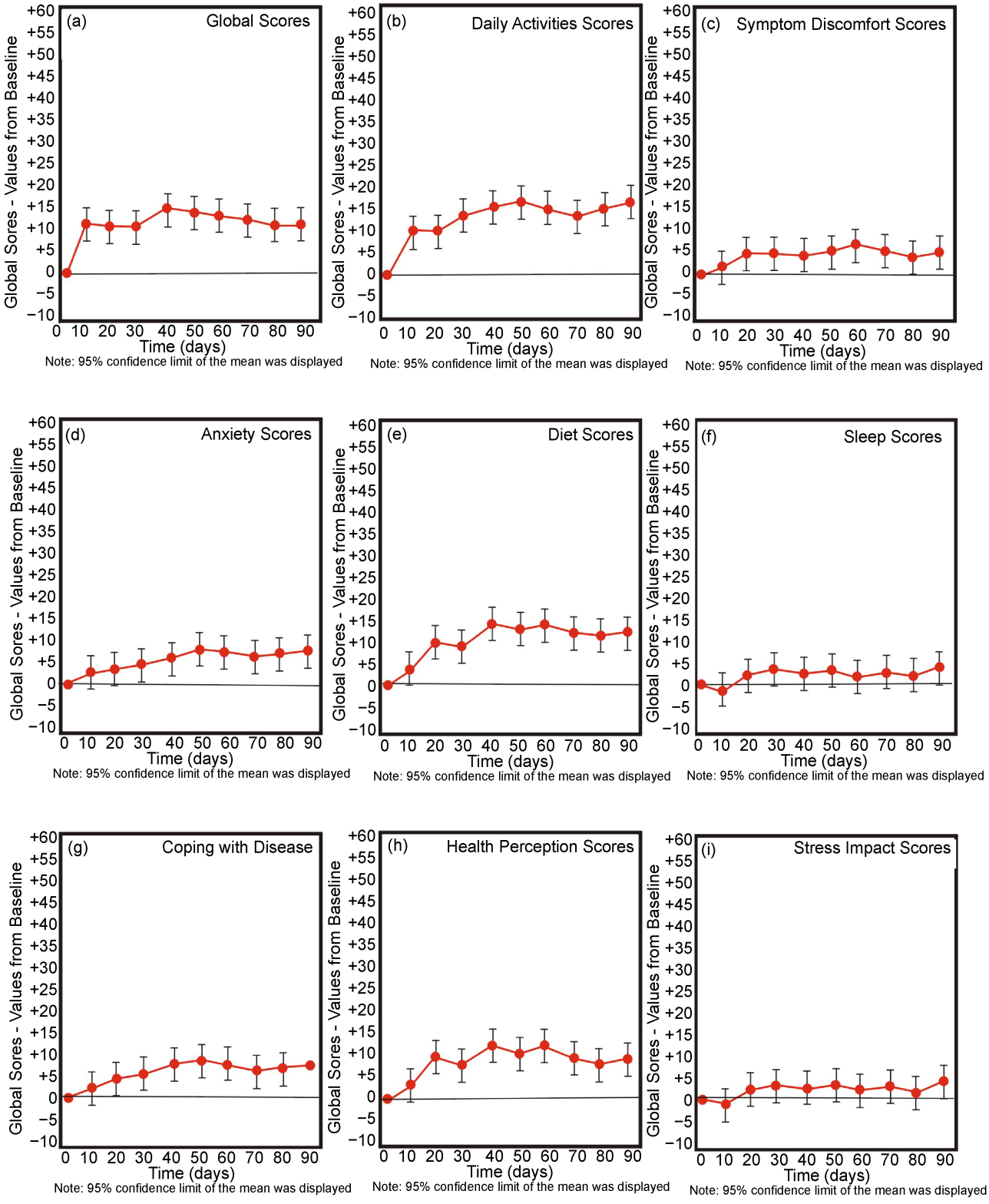

Figure 1. Digestive disorders questionnaire results. Combined results of the study (Global Scores) and subparts of the study over a 90-day period are presented. Results indicate normalized scores (mean scores minus baseline scores; brackets indicate 95% confidence levels of the means). Improvements in normalized scores are indicated by increases in normalized score values presented in the figure. Panels indicate Combined Global Scores (a), Daily Activities Scores (b), Symptom Discomfort Scores (c), Anxiety Scores (d), Diet Scores (e), Sleep Scores (f), Coping with Disease Scores (g), Health Perception Scores (h), Stress Impact Scores (i).

Table 2. The estimated changes from baseline of the dimension score at each survey time from the GEE models.

The Estimated Changes from Baseline of the Dimension Scores at Each Study–Time during Survey										
Survey time point (days)	DA Estimates (95%CI)	AN Estimates (95%CI)	DI Estimates (95%CI)	SL Estimates (95%CI)	DT Estimates (95%CI)	HP Estimates (95%CI)	CD Estimates (95%CI)	IS Estimates (95%CI)	GS Estimates (95%CI)	Alt GS Estimates (95%CI)
0	0.02 (−0.28, 0.31)	0.02 (−0.2, 0.24)	0.11 (−0.18, 0.4)	−0.06 (−0.28, 0.16)	−0.05 (−0.2, 0.11)	−0.02 (−0.13, 0.08)	−0.05 (−0.27, 0.17)	−0.01 (−0.13, 0.12)	−0.02 (−0.17, 0.12)	−0.02 (−0.17, 0.12)
10	12.53 (6.57, 18.5)	9.79 (4.98, 14.61)	2.6 (−1.54, 6.75)	1.85 (−1.36, 5.06)	3.7 (−0.52, 7.92)	−1 (−4.54, 2.54)	3.62 (−4.06, 11.3)	−1.56 (−6.86, 3.73)	4.71 (2.1, 7.31)	4.66 (2.2, 7.11)
20	11.22 (5.53, 16.91)	9.8 (4.36, 15.24)	5.11 (−0.08, 10.3)	4.68 (0.31, 9.05)	10.65 (5.79, 15.51)	1.46 (−3.25, 6.18)	9.69 (2.91, 16.47)	−1.53 (−6, 2.94)	7.49 (4.15, 10.83)	7.19 (3.96, 10.42)
30	11.27 (4.75, 17.79)	12.19 (5.91, 18.47)	5.54 (0.01, 11.08)	5.42 (0.22, 10.61)	10.12 (5, 15.24)	3.11 (−0.95, 7.17)	5.31 (−1.45, 12.06)	−1.09 (−7.1, 4.91)	7.53 (3.89, 11.18)	7.4 (3.91, 10.89)
40	14.55 (8.52, 20.57)	14.64 (8.99, 20.28)	5.03 (−0.92, 10.97)	7.25 (1.87, 12.64)	15.85 (11.05, 20.66)	2.89 (−1.45, 7.22)	8.54 (1.72, 15.36)	−1.74 (−7.59, 4.11)	9.8 (5.9, 13.7)	9.74 (6.05, 13.43)
50	13.71 (7.13, 20.28)	16.91 (10.22, 23.61)	6.94 (0.69, 13.2)	9.81 (4.62, 15.01)	14.67 (10.08, 19.27)	3.53 (−1.04, 8.1)	10.98 (2.58, 19.38)	2.74 (−3.61, 9.09)	10.94 (6.88, 15)	10.65 (6.78, 14.51)
60	13.14 (6.75, 19.54)	16.03 (9.16, 22.9)	8.76 (2.54, 14.98)	9.68 (3.99, 15.36)	17.12 (11.48, 22.75)	1.42 (−2.98, 5.82)	8.78 (0.7, 16.87)	2.3 (−3.4, 8)	10.73 (6.75, 14.7)	10.74 (6.84, 14.63)
70	12.64 (6.81, 18.48)	14.51 (6.65, 22.37)	7.12 (−0.04, 14.28)	8.12 (2.29, 13.96)	14.16 (8.34, 19.99)	2.09 (−2.55, 6.72)	10.48 (1.7, 19.26)	1.27 (−5.69, 8.24)	9.89 (5.11, 14.68)	9.66 (5.11, 14.2)
80	10.93 (4.52, 17.34)	16.35 (7.66, 25.04)	6.31 (0.37, 12.24)	8.98 (3.78, 14.17)	13.11 (7.09, 19.13)	0.9 (−3.64, 5.44)	9.55 (2.11, 17)	0.74 (−7.84, 9.31)	9.44 (5.25, 13.64)	9.02 (4.87, 13.16)
90	10.88 (3.16, 18.6)	17.25 (8.84, 25.66)	7.13 (0.7, 13.55)	10.15 (4.11, 16.18)	13.83 (7.31, 20.35)	3.9 (−1.07, 8.87)	8.08 (−1.73, 17.88)	2.6 (−4.73, 9.94)	10.19 (5.66, 14.72)	9.83 (5.42, 14.24)

Abbreviations: DA, daily acitivites; AN, anxiety scores; DI, diet scores; SL, sleep scores; DT, symptom discomfort scores; HP, health perception scores; CD, coping with disease scores; IS, impact scores; GS, global scores; Alt GS, alternate global scores; CI, confidence intervals.

patients' impression of overall global change in symptoms and QOL showed significant improvements in satisfaction with the test supplement (moderately better improvements in symptoms and QOL, or a score of 4.8 ± 0.169, $p < 0.0001$).

3.4. Safety of the Study

There were no safety issues that came up during the clinical trial. In support of this the NutrEval™ diagnostic blood evaluation panels showed no significant changes in blood chemistry and levels of blood antioxidants, vitamins, minerals, essential fatty acids, probiotics, pancreatic enzymes, and amino acids during the study.

4. Discussion

The dietary test supplement used in the present clinical study (now called GI Regenerate™) has been used for years in China and other countries to treat patients with a variety of gastrointestinal disorders and diseases [14]-[19]. These clinical studies were dependent on this dietary supplement repairing gastrointestinal damage. To demonstrate the effects of the test dietary supplement on stimulating gastrointestinal epithelial cell survival, growth and regeneration, some

experimental studies were initiated. After excision and *in vitro* culture of organ explants of murine stomach and intestinal tissues in medium containing fetal bovine serum, addition of the test dietary supplement was shown to stimulate epithelial cell survival, growth and differentiation, whereas the cells in explant cultures without the dietary test supplement began to die and never formed viable cell colonies [12] [13].

Consistent with the findings in China on the clinical benefits of using the oral test dietary supplement to treat ulcerative colitis [14], gastroesophageal reflux disease [15], gastric ulcers [16], peptic ulcers [17], GERD [23] and gastrointestinal damage due to ethanol [18] or infection [19] we found that North American patients with a variety of gastrointestinal disorders and symptoms (**Table 1**) responded positively to the test dietary supplement GI Regenerate™. These positive responses were collected using the validated digestive disorders questionnaire of Chassany, *et al*. [20] over a 90-day period. The results indicated that male and female patients with IBS, GERD, Crohn's disease, celiac disease, ulcerative colitis, gastritis, and digestive symptoms, such as abdominal bloating and pain, gastric pain, constipation, diarrhea, fatigue, flatulence, nausea, regurgitation and food allergies and malabsorption, improved significantly during the test period ($p = 0.0183$), with significant QOL improvements in symptom discomfort ($p = 0.0004$), daily activities ($p = 0.029$) and anxiety ($p = 0.018$).

Our results using the validated digestive disorders questionnaire were confirmed in the PGIC exit surveys where patients indicated moderately better improvements in symptoms and QOL ($p < 0.0001$) at the end of the study. Thus we have confirmed the benefits of taking oral capsules of GI Regenerate™ found in previous studies on the improvements in gastrointestinal symptoms in patients with digestive disorders and diseases [14]-[19].

There were no safety concerns that came up during the trial. Patients did not report issues with the GI Regenerate™ oral supplement, and blood chemistry analyses every month during the trial on every subject using the NutrEval™ diagnostic blood evaluation panel did not indicate any abnormalities in levels of blood antioxidants, vitamins, minerals, essential fatty acids, probiotics, pancreatic enzymes, or amino acids during the study. Thus we concluded that the GI Regenerate™ oral supplement was safe and effective for use in treating gastrointestinal symptoms in early adults to the elderly.

Although the results of our clinical study were positive and generally significant statistically, there were obvious limitations of the trial. First, we note that although the numbers of females in our study were sufficient, we had less access to male patients. Thus the numbers of males in our study (10) were much lower than the numbers of females (40). Future studies should contain more balanced numbers of males and females. Also, the study was a preliminary open label study, not a robust, randomized, controlled clinical trial. There are few evidence-based clinical studies using randomized clinical trials on the use of Chinese dietary herbal supplements to treat digestive disorders [25] [26]. The results

presented here should stimulate the organization of a randomized, controlled clinical trial using GI Regenerate™ to test for improvements in symptoms in patients with digestive disorders and diseases.

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Disclosures

Garth L. Nicolson and Robert Settineri are part-time research consultants to Allergy Research Group, Inc., Naturally Plus USA, Inc. and Nutritional Therapeutics, Inc. There are no other disclosures.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Patient Name:
Subject Number:
Email:
Phone number:
Exit date:

Please choose the response below that best describes the overall change in your symptoms and quality of life since you started taking the study supplement.

- ❑ Very Much Better
- ❑ Moderately Better
- ❑ A Little Better
- ❑ No change
- ❑ A Little Worse
- ❑ Moderately Worse
- ❑ Very much Worse

Patient Signature: _____

Date: _____

Figure A1. Patient's Global Impression of Change (PGIC).