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Research Article

Evaluation of the Safety and Efficacy of Herbal Formulation on Gastrointestinal Health - A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

In the current scenario, people have often adopted a sedentary lifestyle with a large amount of fast-food consumption, a lack of a balanced and nutritious diet, etc., which is drastically hampering their gut health. So there is an emerging need for a promising and safe medication for gastrointestinal illnesses that promotes improvement of overall gut health. The present clinical trial aims at generating evidence around the safety and effectiveness of incorporating a phytoconstituents-based product in the management of digestive ailments. This clinical trial was a randomized, double-blind, placebo-controlled trial involving 60 patients with self-described gastrointestinal symptoms, divided equally into two parallel groups. Herbal formulation and placebo treatment were given as 1 tablet twice a day after meals for 3 months. Response to treatment was evaluated from the baseline to the end of the study on the basis of changes in symptom scores for various clinical symptoms like epigastric pain, heartburn, nausea, constipation, etc. Also, the safety and tolerability of the drug were evaluated by monitoring adverse events and hematological, lipid, liver, and renal function tests at baseline and the end of the study. 100% of patients got relief from symptoms like epigastric discomfort, belching, flatulence, fullness of the stomach, abdominal distension, hyperacidity, bloating, and postprandial fullness in 14 days of treatment with herbal formulation. 100% of patients got relief from heartburn, nausea, and vomiting in 7 days of treatment with herbal formulation. Also, 100% of patients got relief from constipation after 90 days of treatment of herbal formulation. There was reduction in rescue medication for 90% of subjects after 90 days of treatment of herbal formulation. While there was no evidence of fluctuation in liver function test, renal function test and lipid profile indicating systemic safety. Therefore, indicating improvement in overall health and quality of life of patients with gastrointestinal discomfort as compared to the placebo treatment.

Keywords: Gastrointestinal Symptoms; Gut Health; Herbal Formulation; Constipation; Quality of Life

Abbreviations

CTRI: Clinical Trial Registry-India; CRF: Case Report Form; GI: Gastrointestinal; LFT: Liver Function Test; MS: Multiple Sclerosis; RFT: Renal Function Test; SPPS: Statistical Package for the Social Sciences

Introduction

Microbes in the gut are an important component of the gut microbiota, which contains more microbes than cells in the human body. The gut is colonized by 10^{14} microbes, which is ten times more than the cell population of the body [1]. The term "gut health" is used in a very general form by food industry. Although it covers multiple positive aspects of the gastrointestinal (GI) tract, such as the effective digestion, and absorption of food, the absence of GI illness, normal and stable intestinal microbiota, effective immune status, and a state of well-being [2].

The GI barrier adjacent to the GI microbiota appears to be the key to understanding the complex mechanisms that maintain gut

health. Bacteria in the gut provide essential nutrients, produce vitamin K, aid in digestion, promote angiogenesis and nerve function in the body [3]. Infants gut microbiota differs greatly from adult microbiota in terms of composition and temporal pattern. This microbiota stabilizes to adult- like profile around the age of one year, usually after introduction of solid foods [4].

Gut bacteria play an important role in human health by contributing to the gut defense system and maintaining its function, while the composition of this bacterium can be affected by the host. Any impairment of the GI barrier can increase the risk of developing infectious, inflammatory, and functional GI diseases, as well as extra intestinal diseases such as obesity, diabetes, and even cancer [5].

The composition of the gut bacterial community in the stomach and colon is different, which is mainly due to distinct physicochemical conditions, such as intestinal motility, pH value, host secretions (e.g., gastric acid, bile, digestive enzymes, and mucus), redox condition, nutrients, and the presence of an intact ileocaecal valve. Apart from this, they can also be influenced by many factors, such as the use of antibiotics, aging, illness, stress, bad dietary habits, and lifestyle [6].

Symptoms of an unhealthy gut can include gas, bloating, constipation, diarrhea, headaches, memory loss, fatigue, chronic pain, difficulty sleeping, cravings, bad moods. These signs if left unattended, can lead to autoimmune diseases like Hashimoto's disease, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis (MS), which causes the immune system to attack different parts of the body. Thus, it is very important to keep a close check on the gut microflora and overall gut health [7].

Polyherbal formulations are often effective in managing gut health without side effects. A comprehensive clinical trial with actual clinical outcomes are very useful while integrating the phytoconstituents-based product for the treatment of digestive ailments.

Material and Method

Study objectives

The primary objectives of the study were to assess changes in clinical symptoms such as epigastric discomfort, heartburn, nausea, vomiting, belching, flatulence, fullness in stomach, abdominal distension, etc. on a 5-point Likert scale from baseline to end of the study. The secondary objectives of the study were to evaluate percentage responders compared to placebo from baseline to end of the study, compliance of the subject to the drug treatment, reduction in requirement of rescue medication. Also, the safety and tolerability of the formulation were assessed using monitoring of adverse effects, biochemical parameters like - hematology, LFT, RFT, lipid profile, and vitals examination at baseline and end of the study.

Inclusion criteria

Males and females between 18-60 years of age (both inclusive) with self-described any of the gastrointestinal symptoms like epigastric discomfort, heartburn, nausea, vomiting, belching, flatulence, fullness in stomach, abdominal distension, etc. were included in the study. The subjects included in the study were not consuming any prebiotics or probiotics and were willing to participate in the study.

Exclusion criteria

Subjects having any major critical illness or actively having gut infections were not included in the study. Pregnant and lactating women were also excluded from the study. subjected who were not willing to provide inform consent and as per the discretion of investigator not eligible were excluded from the study.

Methodology

Healthy adult subjects of 18 to 60 years of age with self-reported unsatisfactory bowel habits were screened for eligibility criteria. On screening visit, a written informed consent was obtained from subject confirming participation in the study. Subject's medical and medication history, demographic details, laboratory examination, vitals, current medication if any were noted in the case record from (CRF). The subjects were considered for further evaluation as per the inclusion and exclusion criteria.

On baseline visit, subject recruited in the study were randomized to the respective study groups as per the computer generated randomization list. Subjects from the treatment and placebo group received polyherbal formulation and placebo formulation, respectively for 1 month. Subjects were advised to consume 1 tablets of investigational product (either herbal tablet or placebo tablet as per randomization schedule) twice a day after meals for 3 months (90 days).

Investigational product compliance will be assessed on each and every follow up visit based on subject diary. Subjects were called to their respective study sites for follow up visits on Days 30, 60, and 90, whereas symptoms assessment on days 7 and 14 were done through telephonic follow-up. On baseline and every follow up Visit, subjects were evaluated for safety and efficacy parameters.

After completion of 3 months of study treatment, subjects were asked to stop investigational product and take advice of investigator for further treatment. Post-study safety evaluations were done. Subject were closely monitored for any adverse event starting from baseline visit till the end of the study visit.

Intervention and dosage

The key ingredients of polyherbal formulation (GP/PROD/2021/003) are standardized and fortified extracts of *Terminalia Chebula* Ext.(Harda), *Operculina turpethum* ext. (Trivrit), *Plantago ovata* ext. (Isabgol), *Phyllanthus emblica* ext. (Amla), *Rheum rhabarbarum* ext. (Rhubarb), etc. Subjects from test and placebo groups were advised to consume 1 tablet twice a day after meals for 3 months of polyherbal (GP/PROD/2021/003) and placebo formulation, respectively.

Sample size

The said clinical trial is exploratory study so as per the clinical experience, we chose to enroll around 60 subjects to validate the primary and secondary outcomes. Further a clinical trial with more number of subject with controlled confounders is warranted to generalize the results.

Randomization

We intended to complete 60 subjects at the end of the study. We screened 65 subjects of which two did not fit in the inclusion criteria hence, were considered screen failure. Total of 63 subjects entered the randomization, 3 were considered dropout (one from test and two from placebo group) due to lost to follow-up. We got 60 evaluable completer cases. The patient disposition is depicted in figure 1. This was a randomized study wherein all the subjects were randomly allocated (as per computer generated randomization list) to either one of the treatment arms i.e., polyherbal formulation and placebo in 1:1 ratio. We received randomization schedule from qualified statistician, investigator enrolled the participants to respective study groups. The informed consent was obtained from subjects. Identical placebo in terms of color, size, shape, weight was followed in order to keep both investigator as well as the subject blind of which medication was being received. The concealment of the investigational products was achieved by numbering the containers as per the subject's identity numbers and randomized accordingly. Statistical analysis has been done by using SPSS version 10.0.

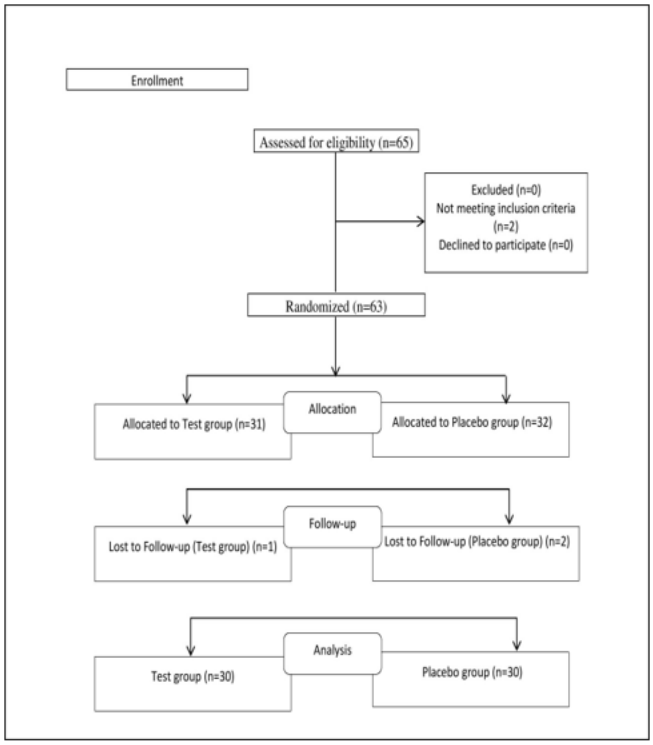


Figure 1: CONSORT diagram for the study.

Results and Discussion

Demographic characteristics

There were 63 subjects enrolled into study and 60 subjects completed the study and data is analyzed (Figure 1). There were 30 evaluable subjects in each group. Both groups were comparable in their gender distribution and mean age. The details are presented in table 1.

Change in clinical symptoms

Change in epigastric discomfort between groups

In this study, at baseline visit all the patients from both the groups had symptoms of epigastric discomfort ranging from mild

Parameter	GP/PROD/2021/003 (N = 30)		Placebo (N = 30)	
Group/ Gender #	Male (n = 16)	Female (n = 14)	Male (n = 12)	Female (n = 18)
Age* (years)	41.44 ± 8.66	42.57 ± 10.5	40.58 ± 12.16	42.89 ± 10.57

Table 1: Demographic details.

Data analyzed by * student t test, # Chi square test. Not significant p < 0.05.

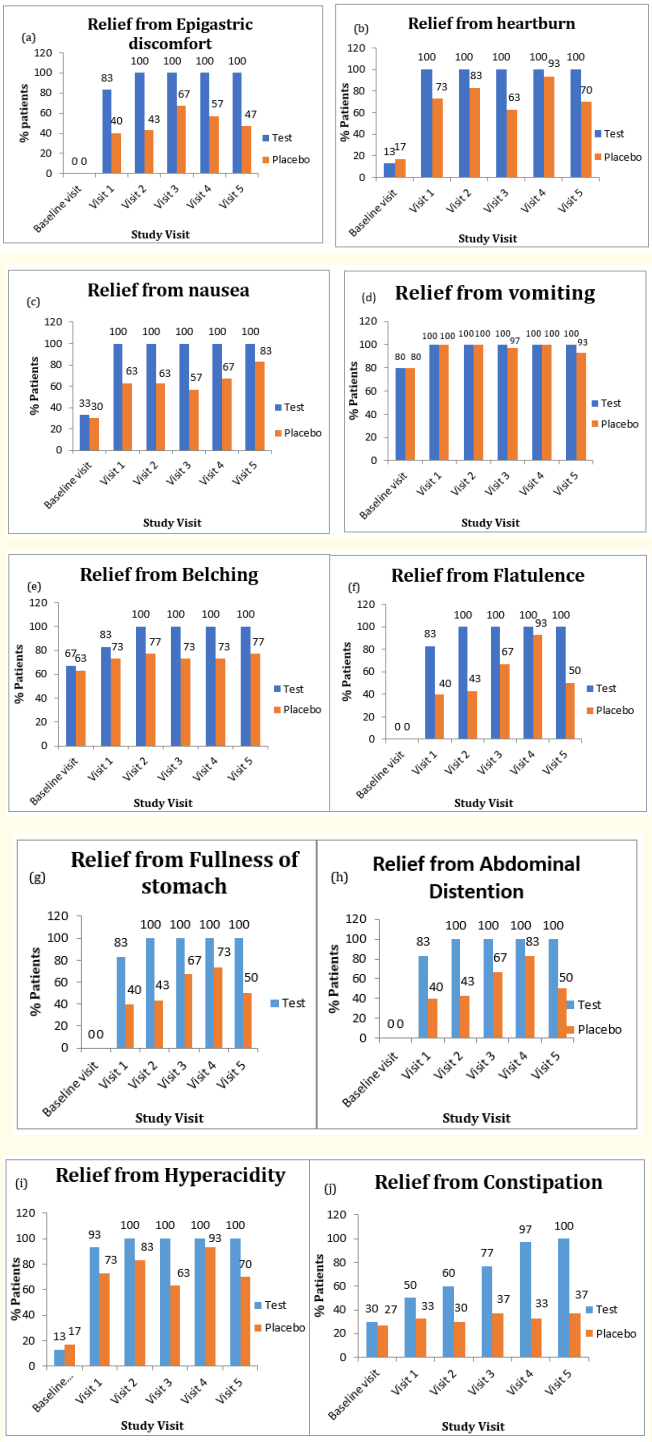
to moderate scores. At visit 1, around 83% of patients from test group had no symptoms of epigastric pain whereas it was only 40% of patients in placebo group. At Visit 5, 100% of patients from test group had no symptom of epigastric pain which was significantly more as compared to 47% in placebo group. Thus the herbal formulation GP/PROD/2021/003 showed a significantly consistent and better effect in alleviating epigastric pain as compared to placebo group (Table 2) (Figure 2a).

Clinical symptom score	Baseline visit		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
	Test No. (%)	Placebo No. (%)	Test No. (%)	Placebo No. (%)	Test No. (%)	Placebo No. (%)	Test No. (%)	Placebo No. (%)	Test No. (%)	Placebo No. (%)	Test No. (%)	Placebo No. (%)
Epigastric discomfort	0	0	25* (83)	12 (40)	30* (100)	13 (43)	30* (100)	20 (67)	30* (100)	17 (57)	30* (100)	14 (47)
Heartburn	4 (13)	5 (17)	30* (100)	22 (73)	30* (100)	25 (83)	30* (100)	19 (63)	30 (100)	28 (93)	30* (100)	21 (70)
Nausea	10 (33)	9 (30)	30* (100)	19 (63)	30* (100)	19 (63)	30* (100)	17 (57)	30* (100)	20 (67)	30* (100)	25 (83)
Vomiting	24 (80)	24 (80)	30 (100)	30 (100)	30 (100)	30 (100)	30 (100)	29 (97)	30 (100)	30 (100)	30 (100)	28 (93)
Belching	20 (67)	19 (63)	25 (83)	22 (73)	30* (100)	23 (77)	30* (100)	22 (73)	30* (100)	22 (73)	30* (100)	23 (77)
Flatulence	0	0	25* (83)	12 (40)	30* (100)	13 (43)	30* (100)	20 (67)	30 (100)	28 (93)	30* (100)	15 (50)
Fullness of stomach	0	0	25* (83)	12 (40)	30* (100)	13 (43)	30* (100)	20 (67)	30* (100)	22 (73)	30* (100)	15 (50)
Abdominal distension	0	0	25* (83)	12 (40)	30* (100)	13 (43)	30* (100)	20 (67)	30* (100)	25 (83)	30* (100)	15 (50)
Hyperacidity	4 (13)	5 (17)	28* (93)	22 (73)	30* (100)	25 (83)	30* (100)	19 (63)	30 (100)	28 (93)	30* (100)	21 (70)
Constipation	9 (30)	8 (27)	15 (50)	10 (33)	18* (60)	9 (30)	23* (77)	11 (37)	29* (97)	10 (33)	30* (100)	11 (37)
Bloating	0	0	25* (83)	12 (40)	30* (100)	13 (43)	30* (100)	20 (67)	30* (100)	24 (80)	30* (100)	17 (57)
Postprandial fullness	0	0	25* (83)	12 (40)	30* (100)	13 (43)	30* (100)	20 (67)	30* (100)	24 (80)	30* (100)	17 (57)

Table 2: Change in clinical symptoms associated with gut health.

Various clinical symptoms associated with gut health were assessed on 5-point Linkert scale where, Score 0 -No symptoms, Score 1 - Mild symptom (not affecting daily activities), Score 2 - Mild symptom (affecting daily activities), Score 3 - Moderate symptoms (affecting daily activities), and Score 4 - Severe Symptoms.

Data analyzed by * student t test, # Chi square test. Not significant p < 0.05.



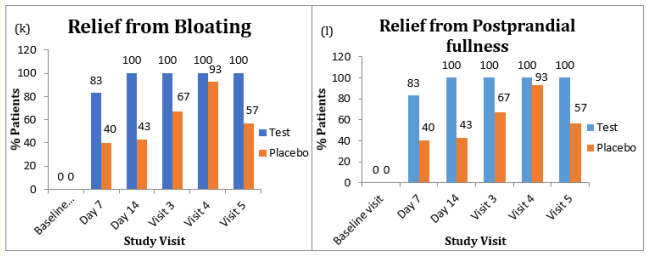


Figure 2: Change in clinical symptoms associated with gut health.

Change in heartburn between groups

At baseline visit, almost 85% of patients from both groups had symptoms of heart burn associated to gastrointestinal disorders ranging from mild to moderate scores. At visit 1, 100% of patients from test group had no symptoms of heartburn, whereas it was only 73% of patients in placebo group. At Visit 5, 100% of patients from test group had no symptom of heartburn which was significantly more as compared to 70% in placebo group. Thus the herbal formulation GP/PROD/2021/003 showed a significantly consistent and better efficacy in curing heartburn as compared to placebo group (Table 2) (Figure 2b).

Change in nausea symptoms between groups

In present study, at baseline visit 67% of patients from test group and 70% patients from placebo group had mild symptoms of nausea. After initiation of respective treatments, patients in test group were completely relieved from nausea throughout the study duration (i.e. 90 days), whereas only 83% of patients from placebo group had no symptoms of nausea at visit 5 which is significantly less as compared to test group (Table 2) (Figure 2c).

Change in vomiting symptoms between groups

At baseline visit, around 20% patients from both the group had vomiting symptoms associated with gastric distress. In subsequent visits i.e. visit 1, 2 and 4 this symptom was not experienced by any patient in both the groups. However, at visit 3 and visit 5 patients from placebo group experienced recurrence of vomiting symptoms whereas there were no such cases in test group (Table 2) (Figure 2d).

Change in belching symptoms between groups

In this study, at baseline visit 34% of patients from test group and 37% patients from placebo group had mild symptoms of

belching. After initiation of respective treatments, patients in test group were completely relieved from bleaching at visit 2 and throughout the study duration (i.e. 90 days) whereas only 76% of patients from placebo group had no symptoms of belching at visit 5 which is significantly less as compared to test group. Thus indicating that herbal formulation (GP/PROD/2021/003) has better and consistent effect on relieving belching symptoms in patients with poor gut health as compared to placebo group (Table 2) (Figure 2e).

Change in flatulence and fullness of stomach between groups

At baseline visit, all the patients from both the groups had symptoms of flatulence and fullness of stomach ranging from mild to moderate scores. At visit 1, around 83% of patients from test group had no symptoms of flatulence or fullness of stomach, whereas it was only 40% of patients in placebo group. At Visit 5, 100% of patients from test group had no symptom of flatulence or fullness of stomach which was significantly more as compared to 50% in placebo group. Thus the herbal formulation GP/PROD/2021/003 showed a significantly consistent and better effect in alleviating flatulence and fullness of stomach as compared to placebo group (Table 2) (Figure 2f and 2g).

Change in abdominal distention between groups

In the present study, at baseline visit all the patients from both the groups had symptoms of abdominal distention ranging from mild to moderate scores. At visit 1, around 83% of patients from test group had no symptoms of abdominal distention, whereas it was only 40% of patients in placebo group. From visit 2 to the end of study (i.e. Visit 5), 100% of patients from test group had no symptom of abdominal distention which was significantly more as compared to 50% in placebo group at visit 5. Thus the herbal formulation GP/PROD/2021/003 showed a significantly better potency in curing abdominal distention as compared to placebo group (Table 2) (Figure 2h).

Change in hyperacidity between groups

In this study, at baseline visit 87% of patients from test group and 84% patients from placebo group had mild to moderate symptoms of hyperacidity. After initiation of respective treatments, patients in test group were completely relieved (100%) from hyperacidity from visit 2 to throughout the study duration (i.e. 90 days) whereas only 70% of patients from placebo group had no symptoms of hyperacidity at Visit 5 which is significantly less as compared to test group (Table 2) (Figure 2i).

Change in constipation between groups

At baseline visit, around 70% of patients from both the groups had complaint of constipation due to poor gut health. At visit 1, 50% patients from test group experienced relief from constipation whereas only 33% of patients in the placebo group. In subsequent visits, there was a significant improvement in relief from constipation in the test group as compared to the placebo group. At visit 5, 100% of patients from test group had no indication of constipation which is significantly more as compared to 37% of patients from placebo group (Table 2) (Figure 2j).

Change in bloating and postprandial fullness between groups

In this study, at baseline visit all the patients from both the groups had symptoms of bloating and postprandial fullness ranging from mild to moderate scores. At visit 1, around 83% of patients from test group had no symptoms of Bloating and postprandial fullness, whereas it was only 40% of patients in placebo group. At visit 5, 100% of patients from test group had no symptom Bloating and postprandial fullness which was significantly more as compared to 57% in placebo group. Thus the herbal formulation GP/PROD/2021/003 showed a significantly consistent and better effect in alleviating bloating and postprandial fullness as compared to placebo group (Table 2) (Figure 2k and 2l).

Reduction in requirement of rescue medication

In the present study, at baseline visit all the patients from both the groups were in need of rescue medications to manage their gastrointestinal issues like heartburn, nausea, vomiting, fullness of stomach, constipation, etc. After the treatment with herbal formulation, at visit 1 there were 50% of patients who did not require rescue medication whereas there were 20% patients in placebo group. In subsequent visit, the requirement of rescue medication significantly decreased in the patients of test group as compared to placebo group. At visit 5, 90% of patients from test group did not required rescue medication which is significantly more as compare to 46.7% patients in placebo group. Thus indicating that herbal formulation not only cures the gastrointestinal problems but it also significantly reduces the need of rescue medications (Table 3) (Figure 3).

Requirement of rescue medication	Baseline visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Test No. (%)	30 (100)	15* (50)	12* (40)	7* (23.3)	3* (10)	3* (10)
Placebo No. (%)	30 (100)	24 (80)	26 (86.6)	19 (63.3)	20 (66.6)	16 (53.3)

Table 3: Reduction in requirement of rescue medication.

Data analyzed by * Chi square test. * significant $p < 0.05$.

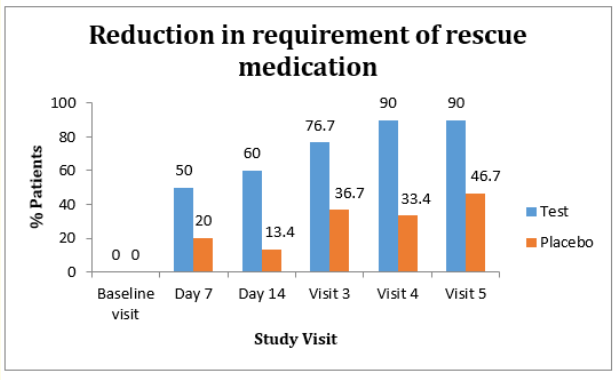


Figure 3: Reduction in requirement of rescue medication.

Changes in % responders compared to the placebo group:

The percentage responders to the given interventions were calculated throughout the study. At visit 1, the % responders in test group increased to 83.33% whereas the placebo group had only 54.58% of responders. The response of patients to the herbal formulation (GP/PROD/2021/003) increased continuously throughout the study, leading to 100% relief from all gastric symptoms at visit 5 which is comparatively more as compared to 61.8% in placebo group (Table 4).

	Baseline visit		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
% responders	Test (%)	Placebo (%)	Test (%)	Placebo (%)	Test (%)	Placebo (%)	Test (%)	Placebo (%)	Test (%)	Placebo (%)	Test (%)	Placebo (%)
Epigastric discomfort	0	0	83	40	100	43	100	67	100	57	100	47
Heartburn	13	17	100	73	100	83	100	63	100	93	100	70
Nausea	33	30	100	63	100	63	100	57	100	67	100	83
Vomiting	80	80	100	100	100	100	100	97	100	100	100	93
Belching	67	63	83	73	100	77	100	73	100	73	100	77
Flatulence	0	0	83	40	100	43	100	67	100	93	100	50
Fullness of stomach	0	0	83	40	100	43	100	67	100	73	100	50
Abdominal distension	0	0	83	40	100	43	100	67	100	83	100	50
Hyperacidity	13	17	93	73	100	83	100	63	100	93	100	70
Constipation	30	27	50	33	60	30	77	37	97	33	100	37
Bloating	0	0	83	40	100	43	100	67	100	80	100	57
Postprandial fullness	0	0	83	40	100	43	100	67	100	93	100	57
Average responders	19.7	19.5	85.33	54.58	96.67	57.83	98.08	66	99.75	78.17	100	61.8

Table 4: Change in % responders compared to placebo.

Safety parameters

Hematological parameters

There were no significant changes observed in hematological parameters in test and placebo group (Table 5).

Laboratory investigation	Test		Placebo	
	Baseline Visit (Mean ± SD)	Day 90 (Mean ± SD)	Baseline Visit (Mean ± SD)	Day 90 (Mean ± SD)
Hemoglobin	13.60 ± 1.61	13.39 ± 1.42	13.35 ± 1.43	13.08 ± 1.24
Total WBC	7080.00 ± 13.58.85	7033.33 ± 1310.26	6483.33 ± 1745.36	6386.67 ± 1724.22
Neutrophil	58.67 ± 8.89	59.43 ± 6.78	59.63 ± 8.19	58.93 ± 7.18
Lymphocyte	34.90 ± 8.48	33.60 ± 6.17	34.33 ± 8.17	33.10 ± 5.31
Eosinophil	2.27 ± 0.91	2.30 ± 0.79	2.03 ± 0.18	2.07 ± 0.37
Monocyte	3.83 ± 0.53	4.03 ± 0.67	4.00 ± 0.00	4.07 ± 0.37
Basophil	0.00 ± 0.00	0.07 ± 0.25	0.00 ± 0.00	0.03 ± 0.18
Hematocrit	39.12 ± 6.41	39.61 ± 5.62	36.42 ± 5.53	37.88 ± 3.68*
RBC Count	4.58 ± 0.75	4.53 ± 0.51	4.32 ± 0.61	4.46 ± 0.43*
MCV	86.24 ± 7.54	86.21 ± 7.47	84.74 ± 9.21	84.53 ± 9.18
MCH	29.98 ± 3.41	30.02 ± 3.37	30.27 ± 3.72	30.48 ± 3.86
MCHC	35.06 ± 3.28	35.20 ± 3.29	35.75 ± 2.42	35.85 ± 2.45
Platelet Count	256600.00 ± 59704.79	256600.00 ± 59110.42	261900.00 ± 73761.19	261930.00 ± 73683.54

Table 5: Change in Hematological parameters between groups.

Compliance of subjects to the drug treatment

The compliance of subjects to the given intervention (i.e. herbal formulation or placebo group) was assessed throughout the study. It was observed that all the patients from both the groups showed 100% compliance to the given treatments.

Adverse effect profile

In the given study, 6 patients from test group experienced adverse event of loose motion due to incorporation of herbal formulation whereas no such case was observed in placebo group. The incidence of loose motion was managed by administration of rescue medication (Lomotil 2 mg). Other adverse events like cough, headache, fever, menstrual pain, cough and cold were also observed. These were resolved within 2-3 days without any rescue medication. All these symptoms were mild in nature and got completely resolved.

Change in lipid profile between groups

There were no significant changes observed in lipid profile in test and placebo group (Table 6).

Laboratory Investigation	(Mean ± SD)			
	Test		Placebo	
	Baseline Visit	Visit 5	Baseline	Visit 5
Total Cholesterol	176.95 ± 41.88	150.57 ± 21.24	166.84 ± 43.01	141.55 ± 26.55
Triglycerides	134.33 ± 41.46	134.63 ± 39.61	127.50 ± 47.68	127.63 ± 46.62
HDL Cholesterol	40.60 ± 6.26	40.13 ± 5.40	41.97 ± 6.52	41.03 ± 7.16
LDL Cholesterol	109.49 ± 39.31	83.51 ± 21.12	99.38 ± 39.44	74.99 ± 24.49
VLDL Cholesterol	26.87 ± 8.29	26.93 ± 7.92	25.50 ± 9.54	25.53 ± 9.32
TC/HDL Ratio	4.43 ± 1.11	3.80 ± 0.62	4.00 ± 0.94	3.50 ± 0.67

Table 6: Change in lipid profile between groups.

Change in Liver function test parameters between groups

There were no significant changes observed in liver function test parameters in test and placebo group (Table 7).

Laboratory Investigation	(Mean ± SD)			
	Test		Placebo	
	Baseline Visit	Visit 5	Baseline	Visit 5
Bilirubin Total	0.48 ± 0.27	0.49 ± 0.27	0.52 ± 0.31	0.55 ± 0.30
Bilirubin Direct	0.14 ± 0.08	0.17 ± 0.08	0.12 ± 0.04	0.15 ± 0.08
Bilirubin Indirect	0.34 ± 0.23	0.32 ± 0.23	0.40 ± 0.30	0.40 ± 0.28
SGOT	22.97 ± 9.08	23.07 ± 7.81	20.70 ± 6.81	20.23 ± 5.53
SGPT	21.33 ± 7.90	22.50 ± 8.16	21.50 ± 8.08	23.30 ± 7.37
Alkaline Phosphatase	86.23 ± 24.18	84.20 ± 23.08	97.70 ± 23.00	95.37 ± 20.60
Total Protein	6.99 ± 0.72	7.22 ± 1.01	6.80 ± 0.68	6.87 ± 0.49
Albumin	4.02 ± 0.29	3.96 ± 0.26	3.91 ± 0.31	3.85 ± 0.30
Globulin	2.92 ± 0.54	3.26 ± 1.00	2.71 ± 0.55	3.02 ± 0.44
A/G Ratio	1.43 ± 0.26	1.28 ± 0.27	1.50 ± 0.29	1.30 ± 0.23

Table 7: Change in Liver function test parameters between groups.

Change in Renal function test parameters between groups

There were no significant changes observed in renal function test parameters in test and placebo group (Table 8).

Laboratory Investigation	(Mean ± SD)			
	Test		Placebo	
	Baseline Visit	Visit 5	Baseline	Visit 5
Urea	21.40 ± 5.56	22.03 ± 4.80	20.47 ± 5.28	21.47 ± 3.99
Creatinine	0.84 ± 0.19	0.90 ± 0.26	0.78 ± 0.14	0.88 ± 0.20*
Uric Acid	4.50 ± 1.41	4.46 ± 1.32	4.75 ± 1.81	4.65 ± 1.53

Table 8: Change in Renal function test parameters between groups.

Conclusion

Gut health is considered as the foundation of well-being of the individual. The good gut microbiome includes balance between the good (helpful) and bad (potentially harmful) bacteria and yeast in person's digestive system. In fact, it is believed that, 80% of your immune system is in the gut, and the majority of your body's serotonin, too. This means if your gut isn't healthy, then your immune system and hormones won't function, and you will get sick.

The composition of gut microbiome differs according to every individual's food habits. The gut microbiome helps the individual in different ways like; it helps the neonates to digest different healthy sugars present in the breast milk which aids their growth [8]. It also helps to digest different fibers which are important to prevent weight gain and reduce risk of diabetes, heart disease and cancer [9]. The study also suggests that gut microbiome not only helps to control our immune system but it also affects the central nervous system, thus controlling the brain function [10].

It has been largely ignored that non-dietary lifestyle factors affect gut microbiota. Due to the fact that smoking and lack of

exercise are risk factors for colorectal cancer, they have a significant impact on the large bowel and potentially the microbiota as well [11]. Another lifestyle factor, stress, has an impact on colonic motor activity via the gut-brain axis which can alter gut microbiota profiles, including lower numbers of potentially beneficial *Lactobacillus* [12]. Excess energy intake and sedentary lifestyles contribute to obesity. Any shifts in microbial populations caused by obesity may be influenced by exercise (or rather a lack of exercise). Recent research indicates that exercise and diet increase the diversity of gut microbial populations in professional athletes [13] Many other factors such as geographical area, travelling and poor sanitary conditions greatly influence the gut microbiome. Thus it is very important to keep a regular check on the gut health to prevent long term health issues.

The proposed intervention of herbal formulation (GP/PROD/2021/003) consist of proprietary blend of *Terminalia Chebula* Ext.(Harda), *Operculina turpethum* ext. (Trivrit), *Plantago ovata* ext. (Isabgol), *Phyllanthus emblica* ext.(Amla), *Rheum rhabarbarum* ext.(Rhubarb), Rosa ext. (Rose), *Trachyspermum ammi* ext. (Ajwain), *Glycyrrhiza glabra* ext. (Mulethi), Mentha ext. (Peppermint), *Senna alexandrina* ext. (Senna), *Zingiber officinale* ext. (Ginger), *Abelmoschus esculentus* ext. (Okra) and *Spinacia oleracea* ext. (Spinach). These extracts have known properties of gastro kinetic, stool softeners, antimicrobial, antiulcer, anti-diarrheal properties which are very beneficial in improving the gut health [14-24].

In this study the patients with self-described gastrointestinal symptoms like epigastric discomfort, heartburn, nausea, vomiting, belching, flatulence, fullness in stomach, abdominal distension, etc were enrolled. These subjects were randomized to test and placebo group and treated with herbal formulation and placebo resp. for 90 days. During the treatment period they were evaluated for any changes in clinical symptoms such as epigastric discomfort, heartburn, nausea, vomiting, belching, flatulence, fullness in stomach, abdominal distension, etc on a 5 point likert scale. Also the patients were analyzed for parameters like % responders, adverse effect, decrease in need of rescue medication and biochemical parameters.

The symptom of flatulence, bloating, fullness of stomach and postprandial fullness were relieved by visit 2 in 100% of patients in test group. This effect was possible due to presence of ingredients like *Terminalia chebula* which has hydrolysable tannins (gallic acid, chebulagic acid), *Phyllanthus embelica* contains tannins, gallic acid and polyphenols and *Zingiber officinale* contains gingerol which are highly effective in improving these gastric symptoms [25-27].

The issues regarding digestion of food like epigastric discomfort and abdominal distention were cured by visit 2 in 100% of patients in test group due to high dietary fiber contents in ingredients like Okra, Ginger and Spinach which aids in digestion [28,29].

Okra pods contain mucilaginous properties with fiber which bind toxins in gut and lubricate the large intestines. This ensures effortless and normal bowel movement due to its natural laxative property. Also it contains probiotics which helps in biosynthesis of the vitamin B complex that aids to increase the population of good gut bacteria [30].

The constipation symptom was cured in 100% of patients in test group by visit 5 whereas there were only 37% of patients in placebo group. This activity was seen due to laxative properties of Isabgol and Senna [31]. Instant relief from constipation was not observed in the patients with the use of herbal formulation (GP/PROD/2021/003) as that of other marketed laxatives, but the constipation was relieved due to relief from other concomitant digestive issue which results in irregular bowel movement. Also this indicates that herbal formulation (GP/PROD/2021/003) is safe for long term use due to its non-habit forming properties.

Also the symptoms like heartburn, nausea, vomiting were relieved in 100% of patients in 7 days (i.e. visit 1) and symptoms like belching and hyperacidity were also relived by visit 2 in test group whereas there were only around 60-70% patients in placebo group.

The herbal formulation (GP/PROD/2021/003) given to test group has constituents like amla, rose and glycyrrhiza which are well known traditional food remedies used to cure amlapitta [32,33]. The polysaccharides released from the root of licorice plays an inhibiting role in *H. pylori* adhesion to gastric mucosa thus leading to anti-ulcer and antacid activity [34] While rose oil can ameliorate inflammatory symptoms of gastritis [35]. Thus all these ingredients act synergistically in relieving the gastrointestinal complaints by not only relieving the symptoms but also curing the root cause of gastric issues.

All the patients were compliant to both the treatments throughout the study duration. Also the percentage responders in the test group was 100% as compared to only 61.8% in the placebo group. Thus indicating better response of patients to the herbal formulation (GP/PROD/2021/003) as compared to the placebo treatment.

It was also observed that during baseline visit all the patients from both the groups needed rescue medication to manage their symptoms. This number greatly reduced to 10% of patients in test group which was significantly lower as compared to 53.3% of patients in placebo group by end of study. Thus it indicates that patients with the treatment of herbal formulation (GP/PROD/2021/003) had better relieve from all the symptoms thereby decreasing the need of rescue medication.

It was also observed that there were no significant changes in hematological profile, liver function test, renal function test and lipid profile in both the groups. Thus indicating that, the intended Herbal formulation (GP/PROD/2021/003) is safe for the treatment of gastrointestinal complication.

It can be concluded from the study that Herbal formulation (GP/PROD/2021/003) is safer and effective option in treating various gastrointestinal complaints and thereby improving the overall gut health and quality of life of patients.

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Dr. Shridhar J. Pandya and Dr. Chetan H. Savaliya are directors in GPlife Healthcare Pvt. Ltd. Other authors declare non competing interests. Authors received funding from GPlife Healthcare Pvt. Ltd.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dr. Shridhar J. Pandya conceived and designed the study, Dr. Chetan H. Savaliya collected and analyzed the data, Dr. Dheeraj H. Nagore wrote and finalized manuscript. All authors have read and approved the manuscript for publication.

Compliance with Ethics Guidelines

We conducted a randomized controlled trial involving patients with self-described gastrointestinal symptoms recruited from the outpatient department of Lokmanya Medical Research Centre, Lokmanya Hospital, Chinchwad, Pune; Atharva Multispecialty Research Centre, New Sanghvi, Pune. The study was approved by Institutional Ethics Committee, Lokmanya Medical Research Centre, and was registered with the Clinical Trial Registry of India (CTRI/2022/01/039174).

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