

# Functional Abdominal Pain of Children: Therapy with Bacillus Coagulans GBI-30, 6086 and Insight into Its Probiotic Properties

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## Authors' contributions

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Probiotics are effective in the treatment of functional gastrointestinal disorders in adults but there is lack of enough clinical evidence in children.

**Aim:** To evaluate effectiveness of Bacillus Coagulans GBI-30, 6086 along with digestive enzymes in the treatment of childhood functional abdominal pain (FAP).

**Methods:** Children with FAP, based on the Rome IV criteria ( $n = 95$ , aged 5-16 years), received Bacillus Coagulans GBI-30, 6086 along with digestive enzymes from a commercially available preparation - Tummysoft® for three weeks. Treatment response was assessed by improvement in the Quality of Life in Reflux and Dyspepsia Questionnaire (QOLRAD) score and Global Overall Symptom (GOS) scale.

**Results:** Patients diagnosed with FAP upon receiving a 3-week treatment with Bacillus Coagulans GBI-30, 6086 along with digestive enzymes, registered statistically significant improvement in both QOLRAD (Baseline,  $30.27 \pm 5.95$ ; 10<sup>th</sup> Day:  $108.39 \pm 7.06$ ; 21<sup>st</sup> day:  $173.71 \pm 6.71$ ,  $P=0.00$ ) and GOS scale (Baseline,  $3.10 \pm 0.37$ ; 10<sup>th</sup> Day:  $2.15 \pm 0.73$ ; 21<sup>st</sup> day:  $1.00 \pm 0.00$ ,  $P = 0$ ) signifying the efficacy of the probiotic in FAP.

**Conclusion:** Bacillus Coagulans GBI-30, 6086 along with digestive enzymes from a commercially available preparation - Tummysoft® was found to be effective in the treatment of childhood functional abdominal pain (FAP).

**Keywords:** Functional abdominal pain; probiotic; bacillus coagulans; quality of life in reflux and dyspepsia questionnaire (QOLRAD) scores, global overall symptom (GOS) scale.

## 1. INTRODUCTION

Abdominal pain that cannot be explained by any visible or detectable abnormality, after a thorough physical examination and appropriate testing, is known as Functional Abdominal Pain (FAP)[1]. Functional abdominal pain (FAP) is a subtype of functional gastrointestinal disorder (FGIDs) among school-aged children[2]. It has a prevalence of 10% amongst all causes of abdominal pain in children. Around 60% of all FGIDs account for FAP[3]. Recurrent Abdominal Pain (RAP) has been classified etiologically into two broad groups, Organic & Functional. Functional group contributes almost 90% of RAP cases[4]. Functional Abdominal Pain has been reported to occur in 10-15% of children aged between 4 and 16 years, globally[3]. In India, the prevalence of FAP ranges from 8.2% to 11%[5]. FAP is associated with substantial healthcare utilization, reduced quality of life, increased absenteeism of child from school and parents from work. This finally leads to a burden on the family healthcare with lack of proper therapeutic strategies in place.

The pathophysiology of FAP as well as other pain related FGIDs is attributed to abnormal gastrointestinal motility, altered brain-gut interaction, visceral hypersensitivity, psychosocial disturbance, low-grade inflammation, and alteration in gastrointestinal microbiota[6]. As pathophysiology of these disorders is ill understood, treatment of FAP in children remains a clinical challenge. An array of pharmacological and non-pharmacological therapies has been studied, but they are unable to provide substantial therapeutic effect in FAP. Studies have shown altered gastrointestinal microbiome in patients with FGIDs. Abnormal gastrointestinal microbiome may not only affect epithelial permeability & intestinal immune function but also affect central and enteric nervous system[7]. There is enough clinical evidence to substantiate the involvement of gut-brain interaction contributing to the development of FGIDs and thereby FAP[7]. Abnormal gastrointestinal microbiota in patients with FGIDs

may be either a cause or a consequence of pathophysiological mechanisms such as gastrointestinal motility and secretion[8].

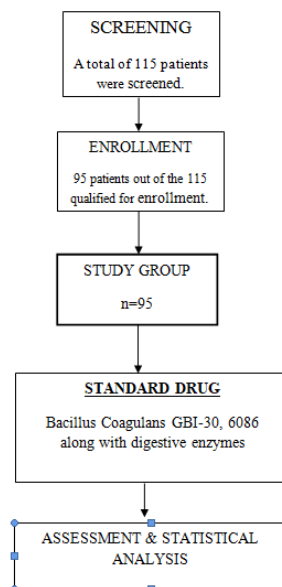
Probiotics are defined by the World Health Organization as “live microorganisms, when administered in adequate amounts; confer a health benefit on the host”[9]. Recently role of probiotics in human health has been the mainstay of research. This is attributed to excellent performance of probiotics in preventing and alleviating diseases, and increasing desire amongst clinicians and patients for natural therapies. Presently probiotic microorganisms have mainly focused on the treatment of gastrointestinal conditions, with traditional probiotics, such as *Streptococcus spp.*, *Lactobacillus spp.*, *Propionibacterium spp.*, *Bifidobacterium spp.*, and *Saccharomyces* species[10]. However, these microorganisms mentioned above can hardly survive in an extremely harsh environment. Therefore, spore-forming probiotic microorganisms have attracted the interest of researchers. Some non-pathogenic Bacillus species are being used as probiotics. The survival and stability of these bacteria are considerably better in comparison with other probiotics as a result of spore-forming capabilities. Amongst Bacillus species, Bacillus Coagulans GBI-30, 6086 has been studied for a long time as a potential probiotic. Bacillus Coagulans GBI-30, 6086 is catalase positive, spore-forming, lactic acid-producing, and facultative anaerobic bacterium[11]. During the growth process, Bacillus Coagulans GBI-30, 6086 can decompose glucose, sucrose, maltose, and mannitol to produce L-lactic acid[12]. Compared with other probiotics, Bacillus Coagulans GBI-30, 6086 is more likely to exert its role in the intestinal tract than traditional live probiotics due to its ability to produce spores. B. coagulans can survive from the stomach in the form of spores and germinate in the intestine, thereby exerting its probiotic effect. Bacillus Coagulans GBI-30, 6086 has been granted Generally Recognised As Safe (GRAS) status by the US Food and Drug Administration[13]. Toxicology studies have assessed its safety in

vivo, and a dose as high as  $9.52 \times 10^{11}$  CFUs was shown to be well tolerated and safe in an average 70 kg human[13]. Additionally, whole genomic analysis of *B. coagulans* suggested that the antibiotic resistance related genes in *Bacillus Coagulans* GBI-30, 6086 were not transferrable to other bacteria, and no other genes with potential safety risks were retrieved[14]. The main reason is that compared to other probiotic bacterial strains, the spore-forming nature of *Bacillus Coagulans* GBI-30, 6086 guarantees its vitality and stability. The spores of *Bacillus Coagulans* GBI-30, 6086 are resistant to high temperature food processing such as boiling and baking[15]. Fig. 1 depicts the life cycle of *Bacillus Coagulans*. In stage 1, spores of *Bacillus Coagulans* enter body orally and safely transit to stomach. Mastication is the first step of this stage and has an important influence on the overall digestive process, particularly on the gastric emptying rate. Following enzymatic & mechanical degradation in mouth, spores are transported via esophagus to the stomach by peristalsis. The presence of gastric juices and bile in the stomach make germination of the *B. coagulans* spore difficult. The first phase will take approximately three hours. In stage 2, after passing through the stomach, the spores begin to germinate in the duodenum and proliferate in the upper part of the small intestine. A nutrient-rich environment with a low microbial load determines spore germination.

Usually, the residence time of *Bacillus coagulans* in the small intestine ranges from 2 to 5 hours. Lastly, in stage 3, live *Bacillus coagulans* will travel down to the large intestine and sporulate in the lower part of colon.

Animal and preclinical studies of *B. coagulans* have mainly focused on the prevention and treatment of gastrointestinal tract (GIT) disorders, such as irritable bowel syndrome, inflammatory bowel disease, antibiotic-associated diarrhea, and colorectal cancer. Notably, among these disorders, *B. coagulans* has frequently been reported as an effective treatment for IBS in adults. We decided to evaluate *Bacillus Coagulans* GBI-30, 6086 in FAP of children, since there were limited numbers of studies in the paediatric FGIDs category. From the family health care perspective too there were few options for the therapy of FGIDs and FAP. The American Society of Family Physicians recommends *Bacillus Coagulans* administration in FAP and found it to be helpful in alleviating its symptoms. Our clinical study provides deep insights into the physiological characteristics, mechanism of action, efficacy and tolerability of *Bacillus Coagulans* GBI-30, 6086 as well as holds a promise in the newer therapeutic approach towards functional abdominal pain disorder of children.

**CONSORT DIAGRAM**



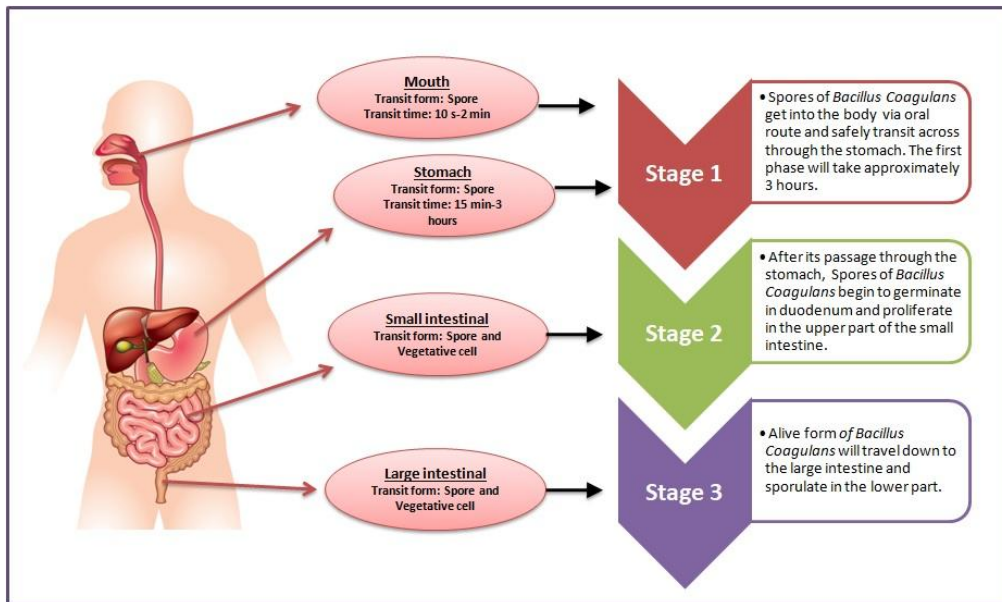


Fig. 1. Life Cycle of B coagulans

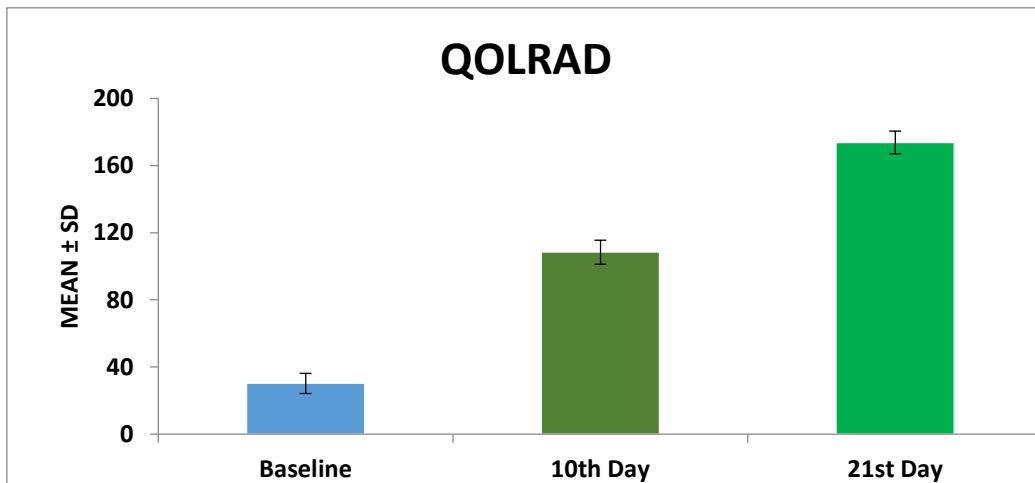


Fig. 2. QOLRAD

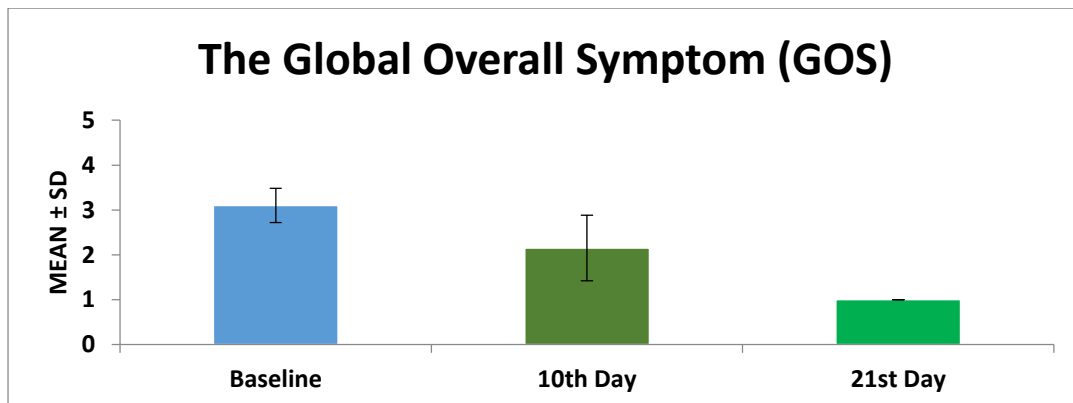


Fig. 3. The Global Overall Symptom (GOS)

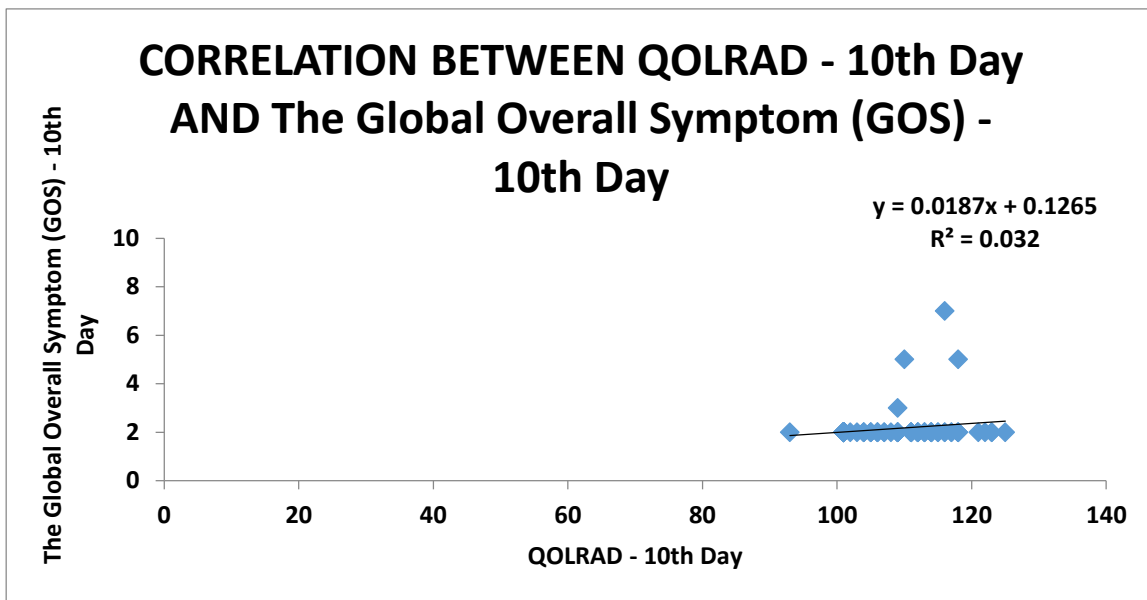


Fig. 4. Correlation between qolrad - 10th day and the Global Overall Symptom (GOS) - 10th day

## 2. MATERIALS AND METHODS

This was a single arm, prospective, interventional study wherein children with FAP, based on the Rome IV criteria ( $n = 95$ , aged 5-16 years), received Bacillus Coagulans GBI-30, 6086 based dry syrup, 5ml twice a day for three weeks. Proper ethical clearance was obtained from independent ethics committee for the study. Rome IV criteria for FGIDs in children includes one or more of symptoms such as postprandial fullness, early satiation, epigastric pain or burning not associated with defecation at least 4 times a month for at least 2 months prior to diagnosis. Further after appropriate evaluation of the FAP, the symptoms weren't fully explained by another medical condition. Children of 5 – 16 years of age suffering from functional abdominal pain were recruited.

Each 5ml of commercially available probiotic Tummysoft® contains 500 million CFU of Bacillus Coagulans GBI-30, 6086, Alpha Amylase 25 mg, Pepsin 10 mg and Lipase 1.5 mg. Tummysoft® was administered at a dose of 5ml twice a day for 3 weeks. Patients or parents of children willing to give a written informed consent form was mandatory for inclusion in the study. Severely malnourished, severely dehydrated, patients with known hypersensitivity for probiotics, patients with chronic or severe respiratory, cardiovascular, CNS, endocrine and other gastrointestinal disorders and history of probiotic administration (one month) were

screened and excluded for every single recruitment.

Treatment response was assessed by improvement in the Quality of Life in Reflux and Dyspepsia Questionnaire QOLRAD score and Global Overall Symptom (GOS) scale. We performed Pearson correlation co-efficient analysis for comparison between the GOS scale and the QOLRAD score. Spearman rank correlation co-efficient were used to assess the relative changes between QOLRAD and GOS scores at 10<sup>th</sup> day and beyond. An increase in QOLRAD and a decrease in GOS scores indicates improvement in clinical outcome for functional abdominal pain. QOLRAD contains 25 questions addressing concerns associated with gastrointestinal symptoms. The questions are rated on a seven-grade Likert scale; the lower the value, the more severe the impact on daily functions. The questions are categorized into five areas: emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning.

The Global Overall Symptom (GOS) scale is a 7-point scale, adapted from a previously validated 5-point scale. The GOS score is self-reported by the patient after the context of the scale, is either read to them, or alternatively, it is read by the patients themselves. In our study it was explained to the children by parents and a proper response was registered. Patients were asked by the parents to grade overall severity of their

dyspepsia symptoms defined as upper abdominal symptoms (located centrally between the breastbone and umbilicus).

### 3. RESULTS

Patients, (n = 95), diagnosed with FAP upon receiving a 3-week treatment with Tummysoft®, registered statistically significant improvement in both QOLRAD and GOS scales.

As per Fig. 2, QOLRAD score is seen to increase progressively, baseline:  $30.27 \pm 5.95$ ; 10<sup>th</sup> Day:  $108.39 \pm 7.06$ ; & 21<sup>st</sup> day:  $173.71 \pm 6.71$ ,  $P=0.00$ . As per Fig. 3, GOS scale is seen to decrease as the treatment progresses, baseline:  $3.10 \pm 0.37$ ; 10<sup>th</sup> Day:  $2.15 \pm 0.73$  & 21<sup>st</sup> day:  $1.00 \pm 0.00$ ,  $P = 0$ . It is to be noted that an increase in QOLRAD and a decrease in GOS scores indicates improvement in clinical outcome for functional abdominal pain. We evaluated the impact of treatment with Bacillus Coagulans GBI-30 6086 based dry syrup along with digestive enzymes, in FAP in children upon five parameters; emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning via QOLRAD score. Considerable statistically significant improvement was noted amongst all parameters within 10 days of treatment with Bacillus Coagulans GBI-30, 6086 based dry syrup, (Table 1,  $P < 0.05$ ). The improvement in emotional distress due to FAP was observed to be; Baseline:  $7.25 \pm 1.6$ , 10<sup>th</sup> day:  $26.17 \pm 2.1$ , 21<sup>st</sup> day:  $41.71 \pm 1.4$ ,  $P < 0.05$ . The improvement in food/drink problems in children arising due to FAP was observed to be; Baseline:  $7.23 \pm 1.5$ , 10<sup>th</sup> day:  $25.95 \pm 1.9$ , 21<sup>st</sup> day:  $41.78 \pm 1.5$ ,  $P < 0.05$ . The improvement in physical & social functioning in children with FAP due to treatment with Bacillus Coagulans GBI-30, 6086 along with digestive enzymes from a commercially available preparation - Tummysoft® was observed to be; Baseline:  $9.59 \pm 1.9$ , 10<sup>th</sup> day:  $34.32 \pm 2.8$ , 21<sup>st</sup> day:  $55.59 \pm 1.9$ ,  $P < 0.05$ . A positive correlation was also noted amongst QOLRAD and GOS scales at 10<sup>th</sup> day of administration of Bacillus Coagulans GBI-30, 6086 along with digestive enzymes from a commercially available preparation - Tummysoft®, as depicted in Fig. 4.

### 4. DISCUSSION

Abdominal pain that cannot be explained by any visible or detectable abnormality, after a thorough physical examination and appropriate testing, is known as Functional Abdominal Pain. The current study focused on newer and

effective treatment strategies for FAP which otherwise is not a well-researched area from both pediatric and family medicine perspectives. Patients diagnosed with FAP as per ROME IV criteria, upon receiving a 3-week treatment with Bacillus Coagulans GBI-30, 6086 along with digestive enzymes from a commercially available preparation - Tummysoft®, registered statistically significant improvement in both QOLRAD and GOS scales. We report positive outcomes with Tummysoft® in FAP of children with five parameters being assessed; emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning. The quality of life of the children enrolled was raised and better satisfaction in terms of the earlier mentioned parameters were reported. The global overall symptom scale reported positive clinical outcome for stomach problems associated with FAP. The digestive enzymes present in Tummysoft® also aid in better resolution of symptoms of FAP which is reflected in GOS scores.

The spores of Bacillus Coagulans GBI-30, 6086 germinate in upper small intestine [16]. In co-operation with the gut microbiome, Bacillus Coagulans GBI-30, 6086 has been shown to increase gut nutrient absorption and availability to aid digestion [17]. Bacillus Coagulans GBI-30, 6086 from a commercially available preparation - Tummysoft® is capable of improving the effective utilization of consumed foods, mainly due to its ability to produce a variety of enzymes (Table 3) [17]. Bacillus Coagulans GBI-30, 6086 can secrete  $\beta$ -galactosidase during growth, which can degrade lactose, found in milk, into galactose and glucose, improving the digestibility of milk and effectively alleviating lactose intolerance [18]. Bacillus Coagulans GBI-30, 6086 strain derived from the commercially available preparation - Tummysoft® promotes digestion of protein and carbohydrates. It has been demonstrated to produce various enzymes to degrade proteins and carbohydrates into smaller peptide molecules and free amino acids, thereby promoting metabolism in the upper part of the small intestine, improving the intestinal environment of the colon, and reducing toxic metabolites. Digestive enzymes produced by Bacillus Coagulans GBI-30, 6086 were known to be active in the gut, and its proteases was found to regulate amino acid metabolism elsewhere in the body [19]. In addition to the production of digestive enzymes, B. coagulans can also produce metabolites such as short chain fatty acids (SCFAs), and vitamins [18]. Bacillus

**Table 1. Parameters of QOLRAD**

Parameters of QOLRAD	Baseline (Mean $\pm$ SD)	10 <sup>th</sup> day (Mean $\pm$ SD)	21 <sup>st</sup> day (Mean $\pm$ SD)	P value
Emotional distress	7.25 $\pm$ 1.67	26.17 $\pm$ 2.13	41.71 $\pm$ 1.41	< 0.05
Food/drink problems	723 $\pm$ 1.55	25.95 $\pm$ 1.93	41.78 $\pm$ 1.59	< 0.05
Physical/social functioning	9.59 $\pm$ 1.94	34.32 $\pm$ 2.81	55.59 $\pm$ 1.96	< 0.05
Sleep disturbance	5.02 $\pm$ 1.31	17.72 $\pm$ 1.71	27.71 $\pm$ 2.26	< 0.05
Vitality	1.18 $\pm$ 0.52	4.29 $\pm$ 0.47	7.00 $\pm$ 0.0	< 0.05

**Table 2. The Global Overall Symptom (GOS) scale**

Please take a few moments to think about the symptoms you have had due to your overall stomach problems in the (specified time period). It is very important for us to get this information. We will be using it as one of the ways to find out if the treatment is helping your stomach problems throughout the study. Overall, how have your stomach problems been over the (specific time period)?

According to the scale below, please indicate the severity of your overall symptoms over the (specified time period)

1. No problem
2. Minimal problem (can be easily ignored without effort)
3. Mild problem (can be ignored with effort)
4. Moderate problem (cannot be ignored but does not influence my daily activities)
5. Moderately severe problem (cannot be ignored and occasionally limits my daily activities)
6. Severe problem (cannot be ignored and often limits my concentration on daily activities)
7. Very severe problem (cannot be ignored and markedly limits my daily activities and often requires rest)

**Table 3. Enzymes produced by *B. Coagulans* species**

Strain	Product
RCS 3	B-galactosidase
KM-1	$\alpha$ - galactosidase
BL174	$\alpha$ - galactosidase
B49	$\alpha$ - amylase
-	Lipase
BL174	Lipase
ZJU318	Lipase
VK11	Lipase
-	Alkaline proteases
PTA-6086	Alkaline proteases

coagulans reduce the production of harmful substances such as amines, stimulate intestinal peristalsis and improve the intestinal metabolic environment, thereby promoting healthy bowel movements and prevent accumulation of toxins[18].

Maria et al investigated and found that 58% of the population suffers from some type of digestive disorder[20]. A lack of optimal digestive function associated with enzyme inadequacy may lead to functional gastrointestinal disorders in children. Digestive enzymes, aid in digestion by facilitating the breakdown of larger molecules present in food, such as carbohydrates, proteins, and fats[21]. This is followed by absorption of

nutrients. Carbohydrates, proteins and fats are initially converted to smaller units by enzymes. By aiding the digestive process, the dyspeptic symptoms are ameliorated. To assist adequate digestion, a combination of different enzymes may have to be supplemented in FAP. Lack of digestive enzyme secretion, hypochlorhydria, pancreatic exocrine insufficiency, biliary disorders results in indigestion and FAP. Children with food intolerances often have special dietary needs. Many have intolerances to proteins such as gluten (in wheat) and casein (in dairy). The incomplete broken down peptides, are improperly absorbed & are the source of intolerances. Dietary enzymes break down these proteins and aid in digestion there by resolving

FAP associated with it. Khandke et al evaluated the efficacy of amylase, protease, lipase, lactase and alpha-galactosidase[22]. Treatment was associated with a significant reduction in frequency and severity of abdominal symptoms: Flatulence, bloating, belching, dyspepsia, feeling of fullness, abdominal discomfort, heart burn and anorexia) (p <0.0001)[22]. The combination of Bacillus Coagulans GBI-30, 6086 along with digestive enzymes in Tummysoft® creates a perfect blend of digestive specific probiotic along with enzymes for the treatment of functional abdominal pain in children.

## 5. CONCLUSION

Bacillus Coagulans GBI-30, 6086 along with digestive enzymes from a commercially available preparation - Tummysoft® was found to be effective in the treatment of childhood functional abdominal pain (FAP). We have registered improvement in quality of life and mitigation as well as complete resolution of abdominal symptoms of FAP with the administration of Tummysoft®. However, larger randomized controlled trials are required to further substantiate our research.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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