

Research Articles

Probiotic food supplement reduces stress-induced gastrointestinal symptoms in volunteers: a double-blind, placebo-controlled, randomized trial

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Abstract

Stress plays an important role in the development of symptoms contributing to disease. Stress induces various disorders with gastrointestinal, physical, and psychological symptoms. Probiotics can help regulate or modulate gastrointestinal functions. The aim of the present study was to investigate the effects of a probiotic preparation (Probio-Stick) on stress-induced symptoms in volunteers. A double-blind, placebo-controlled, randomized study was conducted on volunteers with symptoms of stress. Subjects received a probiotic (Probio-Stick; Lallemand SAS, Saint-Simon, France) containing *Lactobacillus acidophilus* Rosell-52 and *Bifidobacterium longum* Rosell-175 (3×10^9 colony-forming units per sachet stick) or a sensorially identical placebo without probiotics during a 3-week period. The consumption of probiotics significantly reduced 2 stress-induced gastrointestinal symptoms (abdominal pain and nausea/vomiting) for intention-to-treat or per-protocol populations. In contrast, the probiotics did not significantly modify the other physical and psychological symptoms and sleep problems induced by stressful life events for intention-to-treat or per-protocol populations. The results indicate that Probio-Stick can provide a beneficial effect on the gastrointestinal symptoms experienced by individuals affected by chronic stress.

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1. Introduction

Stressful life events play an important role in the genesis and development of functional symptoms [1], altering well-being and quality of life [2,3]. These events produce various symptoms, including gastrointestinal, cardiovascular, social, and psychological. There is a strong correlation between gastrointestinal disorders and psychosocial factors [4]. Gastrointestinal functions can be altered or modulated by different stressful life events [1,5]. In patients with irritable

bowel syndrome (IBS), stress produces diarrhea and constipation through the modification of gastrointestinal motility [5–7]. Gastrointestinal symptoms, such as visceral pain, flatulence, diarrhea, and constipation, are associated with stressful psychosocial events [8–11]. Moreover, the level of chronic stress predicts clinical outcome in patients with IBS and increases the severity of their symptoms [12].

The probiotic concept evolved from a hypothesis first proposed by Russian scientist Elie Metchnikoff in 1908. Investigations in the probiotic field during the past several decades, however, have expanded beyond bacteria isolated from fermented dairy products to those of intestinal origin. Now, probiotics have been defined as nonpathogenic

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microorganisms that, when ingested, exert a positive influence on host health or physiology. Lactobacilli and bifidobacteria are important components of normal intestinal microflora in people of all ages. Lactobacilli also improve lactose tolerance, increase intestinal peristalsis, and accelerate bowel evacuation. Finally, probiotics can alter the volume and/or composition of stool and gas [13] or increase intestinal mucus secretion [14], effects that could influence intestinal handling of its contents and thus modulate symptoms such as constipation and diarrhea. Some evidence in existing literature has generated interest in the consumption of probiotics to relieve gastrointestinal diseases [15]. The interaction between host and commensal microbes can offer important health benefits. This has led to commercial and public interest in probiotics (live microbes principally taken as food supplements). Although the overall impact of probiotics on gastrointestinal symptoms remains unclear, recent studies have shown that lactobacilli prevent visceral pain and stress-induced visceral hypersensitivity in rats [16,17]. However, there has been, as of yet, few data available on the effects of probiotics on stress-induced gastrointestinal symptoms in humans.

Thus, the aim of the present study was to investigate the effects of a probiotic preparation (Probio-Stick; Lallemand SAS, Saint-Simon, France) on stress-induced gastrointestinal and psychological symptoms in volunteers.

2. Methods and materials

A double-blind, placebo-controlled, randomized study was conducted over a 3-week period in healthy volunteers with symptoms of stress ($n = 75$).

2.1. Study participants

To be eligible for this trial, each volunteer needed to meet the following criteria at a screening and baseline visit: (a) volunteers; 18 to 60 years old, male or female; (b) capable of giving informed consent; and (c) affected by daily stress with at least 2 symptoms induced by the stress (anxiety, nervousness, irritability, sleeping problems, gastrointestinal disturbances) during the last month. The center had a statement from the National Ministry of Education, Higher Learning and Research (Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche) to conduct clinical research with healthy volunteers.

2.2. Exclusion criteria

Volunteers were excluded from the study if they had any food allergy, were on a diet, or were affected by any severe systemic diseases. Moreover, volunteers receiving any medical treatment of stress-induced symptoms (such as sleeping pills, antidepressants, or anxiolytics) or individuals having taken such treatment within less than 3 months were also excluded, as were those being weaned off nicotine or having stopped tobacco use within less than 6 months.

Finally, any volunteers who had participated in another clinical trial were ineligible to take part in the study.

2.3. Questionnaire

The questionnaire assessing stress-induced symptoms was designed to identify the physical and psychological discomforts induced by stress. The 62 questionnaire items encompass the following areas: gastrointestinal, cardiovascular, sleep disorders, locomotor systems, physical, emotional and psychological symptoms, intellectual problems, spiritual symptoms, and social aspects. The items are phrased as short, simple statements and scored according a 10-cm visual analogue scale (VAS; maximum score = 10). A global score for each area was determined as the mean of each item.

2.4. Study intervention

One group of volunteers ($n = 37$) received a probiotic (Probio-Stick) containing *Lactobacillus acidophilus* Rosell-52 and *Bifidobacterium longum* Rosell-175 (3×10^9 colony-forming units per sachet) over a 3-week period during the double-blind phase of this study. Another group of volunteers ($n = 38$) received a sensorially identical placebo without probiotics during the same period. Subjects were instructed to ingest the preparation once a day for 3 weeks.

Volunteers completed a questionnaire on stress-induced symptoms at the beginning and the end of the 3-week period. Severity of stress-induced symptoms (gastrointestinal, cardiovascular, social, mental, sleep, and psychological symptoms) was evaluated using a 10-cm VAS (maximum score = 10).

2.5. Statistical analysis

The intention-to-treat (ITT) analysis [18] was performed on all patients ($n = 75$) who underwent randomization and took the product (placebo or probiotics). The per-protocol (PP) analysis was also performed ($n = 64$). The variations of VAS scores were calculated for both groups (probiotics or placebo). Data were collected and analyzed independently of the investigators who did not have access to it or to its analysis. The data were processed using SPSS version 12.0 (SPSS, Chicago, Ill). Quantitative variables were expressed as mean $\pm$ SEM. Comparisons between the placebo and Probio-Stick groups were analyzed using the unpaired Student *t* test [19]. Differences were considered statistically significant for $P < .05$. Data from all enrolled volunteers for rescue treatment were analyzed with an ITT analysis. Volunteers who stopped treatment, had poor treatment compliance, did not follow the protocol, or who were lost during the study were excluded from PP analysis (Fig. 1).

3. Results

A total of 75 healthy volunteers (38 ± 11 years) have been included at visit 1 (V1): 21 males (28%) and 54 females

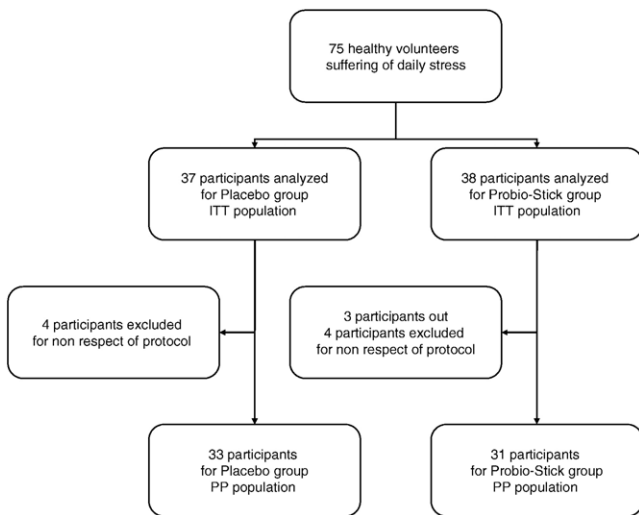


Fig. 1. Trial flowchart.

(72%). The ITT analysis was performed on all patients ($n = 75$) who underwent randomization and took the product (placebo or probiotics; Fig. 1). At the end of the study, 72 participants had completed the trial (4% exited from the study). Eight participants (3 males, 5 females) were not included in the final analysis for noncompliance with the protocol (Fig. 1). Finally, the responses of 64 healthy volunteers were retained for PP analysis: 33 in placebo group and 31 in the Probio-Stick group.

Fig. 2 presents the effect of consuming Probio-Stick or placebo on gastrointestinal symptoms induced by daily stress exposure. The consumption of probiotics reduced 2 stress-induced gastrointestinal symptoms—abdominal pain and nausea/vomiting. The consumption of Probio-Stick resulted in a significant improvement in abdominal pain (-2.59 vs -0.34 for placebo; Fig. 2) and nausea/vomiting (-0.82 vs 0.77 for placebo; Fig. 2). Flatulence and gas production also tended to diminish in the subjects receiving the probiotic supplement (-3.25 vs 1.7 for placebo; Fig. 2). In contrast, the probiotic supplementation did not significantly change the other stress-induced gastrointestinal symptoms, such as dry mouth, swallowing problems, loss of appetite, gastric pain, and rectal pain (Fig. 2). For constipation and diarrhea, the consumption of probiotics did not significantly alter the consistence of stools (constipation, 0.58 vs 0.04 [nonsignificant] and diarrhea, -0.47 vs -1.47 [nonsignificant]; Fig. 2). Similar results were obtained with ITT analysis: only abdominal pain ($P = .032$) and nausea/vomiting ($P = .034$) were significantly improved by probiotic supplementation.

Probiotic supplementation did not significantly modify the other symptoms (cardiovascular, locomotor, and sleep problems) induced by stressful life events for the ITT or PP population (Table 1). In the same manner, social, psychological, intellectual, emotional, and spiritual symptoms induced by stress were not significantly affected by probiotic supplementation for the ITT or PP population (Table 1).

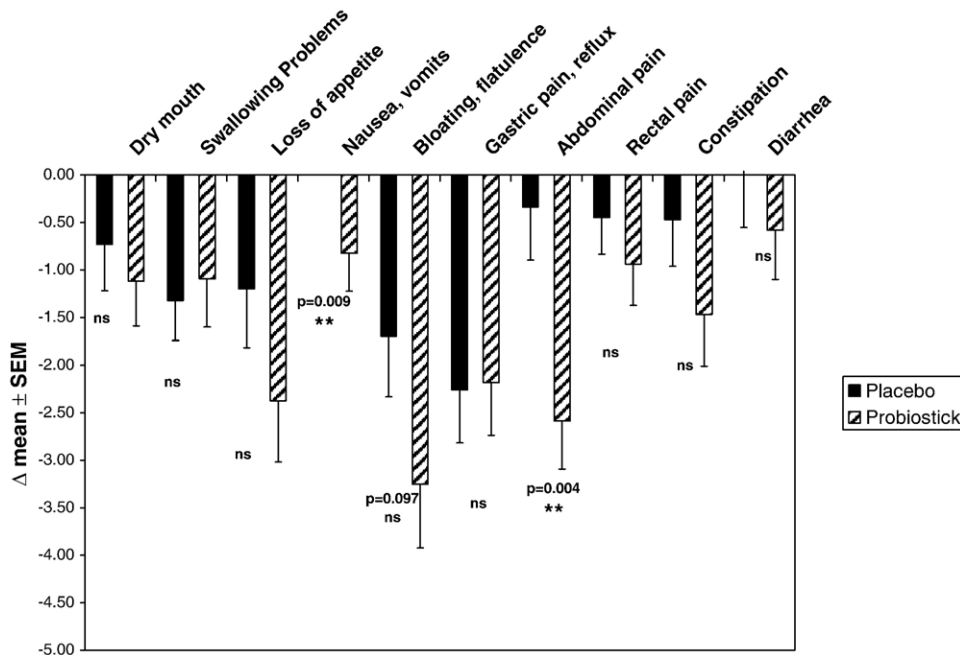


Fig. 2. Effects of Probio-Stick on various stress-induced gastrointestinal symptoms in PP populations. Subjects who stopped treatment, had poor treatment compliance, did not follow the protocol, or who were lost during the study were excluded from PP analysis. Each symptom was evaluated using a 10-cm VAS. The variations of VAS scores were calculated for both groups receiving probiotics or placebo. Comparisons between the placebo ($n = 33$) and Probio-Stick ($n = 31$) groups were analyzed using the Student t test. Differences were considered statistically significant for $P < .05$.

Table 1

Comparison of effects on stress-induced physical and psychological symptoms between the 2 groups for ITT and PP analysis

	Analysis	Placebo	Probio-Stick	P
Cardiovascular symptoms	ITT	-6.45 ± 1.68	-8.66 ± 1.42	NS
	PP	-5.35 ± 0.42	-9.94 ± 0.50	NS
Sleeping symptoms	ITT	-10.11 ± 2.22	-12.86 ± 2.39	NS
	PP	-9.45 ± 2.37	-13.46 ± 2.66	NS
Locomotor Symptoms	ITT	-9.94 ± 1.90	-8.89 ± 1.68	NS
	PP	-8.79 ± 1.76	-10.29 ± 1.95	NS
Physical symptoms	ITT	-3.99 ± 1.04	-5.09 ± 1.04	NS
	PP	-5.19 ± 1.43	-7.31 ± 1.32	NS
Psychological symptoms	ITT	-27.48 ± 3.16	-22.35 ± 2.81	NS
	PP	-25.46 ± 3.30	-22.35 ± 2.81	NS
Intellectual symptoms	ITT	-11.35 ± 1.58	-5.60 ± 1.30	NS
	PP	-10.62 ± 1.55	-6.7 ± 1.49	NS
Spiritual symptoms	ITT	-7.49 ± 1.40	-6.38 ± 1.35	NS
	PP	-8.95 ± 1.38	-5.75 ± 1.56	NS
Social symptoms	ITT	-8.52 ± 1.49	-4.15 ± 1.19	NS
	PP	-6.84 ± 1.36	-4.36 ± 1.31	NS

Each symptom was evaluated using a 10-cm VAS. The variations of VAS scores were calculated for both groups receiving probiotics or placebo. Comparisons between the placebo and Probio-Stick groups were analyzed using the Student *t* test. Differences were considered statistically significant for *P* < .05.

No adverse reactions were reported during the study. The product was safe and well tolerated during the entire period of probiotic supplementation.

4. Discussion

The findings of our study indicate that the combination of probiotics (Probio-Stick: *L. acidophilus* Rosell-52 and *B. longum* Rosell-175) improves stress-induced gastrointestinal symptoms such as abdominal pain, nausea, and vomiting. Furthermore, this treatment was well tolerated and no side effects were noted. The safety of probiotics (lactobacilli and bifidobacteria) that have been used traditionally in food has been confirmed through extensive experience [20,21]. In our study, flatulence and gas production tended to decrease in the subjects receiving the probiotic supplement. Probiotics can have an effect on colonic fermentation, and consequently, reduce the production of gas [13]. In contrast, the probiotic supplement did not improve or affect the other stress-induced gastrointestinal symptoms. The consumption of probiotics did not change stool consistency in subjects with diarrhea or constipation. Similarly, for the other symptoms (cardiovascular, physical, social, psychological, mental, emotional, spiritual, and sleep problems) induced by stressful life events, the probiotic supplement did not affect their severity.

Stress plays an important role in the genesis and development of functional symptoms [5]. Stress affects different gastrointestinal functions, such as esophagus reflux, gastric emptying, gastrointestinal motility, colonic transit, and mucosal function. Stress stimulates the release of corticotrophin-releasing factor from the hypothalamus, resulting in the release of adrenocorticotropin from the

anterior pituitary gland. This, in turn, stimulates the secretion of cortisol from the adrenal cortex [22]. Chronic sustained stress due to adverse life events cause a prolonged increase in cortisol-induced immunosuppression. Experimental stress in animals increases intestinal mucosal permeability [23] and also alters bacterial-host interactions. For its part, psychological stress has been shown to decrease the threshold for the perception of visceral pain. Indeed, clinical and animal studies have demonstrated that visceral hypersensitivity can occur after exposure to stress [24,25].

The human microflora is a complex ecosystem that contributes to the equilibrium of different gastrointestinal functions [15]. The potential beneficial effects of probiotics are due to the modulation of intestinal flora, modification to the mucosa to prevent the adherence of pathogens, and modulation of the immune system [26–28]. The body of evidence supporting the efficacy and mechanisms of probiotics in the prevention or treatment of gastrointestinal disorders has grown significantly in the past 15 years. Probiotics can change colonic fermentation and consequently reduce the production of gas [13]. This can lead to the reduction of certain IBS symptoms. For example, *Lactobacillus plantarum* 299v [29,30] has been shown to relieve some IBS symptoms. In addition, the probiotic mixture VSL no. 3 containing 8 different probiotic species improved abdominal bloating [31] and reduced flatulence associated with inhibited colonic transit in patients with IBS [32]. In contrast, *Lactobacillus GG* [33] and *Lactobacillus reuteri* [34] did not modify or improve IBS symptoms in double-blind, placebo-controlled studies. Moreover, recent studies show that lactobacilli prevent visceral pain and stress- and antibiotic-induced visceral hypersensitivity in rats [16,17,28]. Another recent study reported a beneficial effect on abdominal pain/discomfort in patients with IBS with bifidobacteria supplementation [35] through the normalization of the ratio of an anti- to proinflammatory cytokine, suggesting an immune-modulating role for probiotics. In our study, the probiotic supplement significantly decreased abdominal pain, and we cannot, therefore, rule out such mechanisms for promoting health in humans. In fact, this probiotic supplement could act on the residual intestinal microflora, the epithelial barrier, and the immune system to improve such stress-induced gastrointestinal symptoms as abdominal pain and nausea or vomiting. The consumption of probiotics can contribute to regulating gastrointestinal functions to restore the normal gastrointestinal equilibrium. However, further studies on probiotics are required to define their precise modes of action.

In summary, the consumption of Probio-Stick was found to result in the significant improvement of stress-induced gastrointestinal symptoms (abdominal pain, nausea). At the same time, probiotic supplementation did not significantly affect cardiovascular, physical, social, emotional, psychological, mental, and sleeping symptoms induced by stressful life events. The results indicate that Probio-Stick can indeed

have a beneficial effect on gastrointestinal symptoms in people affected by chronic stress.

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