

Anti-inflammatory Action of the Treated-Yeast, Milmed, Under IBS-IBD Conditions

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Abstract

In order to assess the anti-inflammatory and therapeutic action of the probiotic, treated-yeast Milmed, twelve patients (age range 25-to-79 years) presenting IBS-IBD with a wide range of gut-intestinal symptoms, were studied. Each patient completed a questionnaire outlining demographic characteristics and test items regarding their health issues, both prior to and after the twelve-week period (on three occasions each week) of Milmed intervention. Patients' accounts of their symptom-profiles were quantified and subjected to statistical analyses. It was observed that in comparison with the placebo (administered untreated-yeast) control, the Milmed group reported fewer symptoms, following treatment, as well as also fewer symptoms compared to their pre-treatment report. Untreated-yeast administration to patients did not induce any reduction of IBS-IBD symptoms. There was no correlation between patients' responses regarding symptoms Before and After intervention. It is possible that increasing the number of capsules ingested per week, from 3/week to 1/day, may have provided the patients with greater benefits. Despite certain limitations of this study when taken together with the reported anti-inflammatory propensity of Milmed upon glial and neuronal cell cultures in vitro, these findings imply several useful therapeutic applications for the treated-yeast, Milmed, in the treatment of gut-intestinal conditions, such as IBS-IBD and other related ailments.

Keywords: IBS-IBD; Patients; Symptoms; Milmed; 12 weeks; Improvement; Anti-inflammatory; Questionnaire; Probiotics.

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Abbreviations: IBS-IBD-Irritable bowel syndrome-inflammatory bowel disease; CCFA-Crohn's and Colitis Foundation of America; EHF-Extremely High Frequency; FBD-functional bowel disorder; LPS-Liposaccharide.

Introduction

Gut-intestinal system disorders constitute the more prevalent gastrointestinal disorders, and often include esophageal and swallowing disorders, gastric and peptic ulcer disease, gastroparesis or delayed gastric emptying, functional bowel disorders, chronic idiopathic constipation, irritable bowel syndrome (IBS), ulcerative colitis and Crohn's disease and inflammatory bowel disease (IBD), amongst others [1]. The overlap of Inflammatory bowel disease (IBD) presenting in patients with persistent abdominal symptoms lower or minimal levels of inflammation are frequently described as constituting an overlap of IBD and irritable bowel syndrome (IBD-IBS). The acute phase of IBD presenting inflamed gut with ulcerated mucosa maybe at odds with the mucosa characteristic of IBS. Analysis has presented immune activation, higher gut permeability, increased mucosal serotonin availability, abnormalities of enteric nerve structure and function, and dysbiosis in gut microbiota in IBS, these features are observed in IBD. Studies undertaken to evaluate the prevalence and/or incidence of the IBD-IBS symptom profiles and investigate disorder impact on patient-reported outcomes appear to be defined through their paucity. Notwithstanding, in a cross-sectional investigation within the Crohn's and Colitis Foundation of America (CCFA) Partners Study, involving a total of 1279 (20%) reported a co-existing IBS-IBD diagnoses and applying bivariate analyses and logistic regression

models, associations were sought between the IBD-IBS symptoms and various demographic, disease factors, and patient-reported outcomes including anxiety, depression, sleep disturbances, pain interference, and social satisfaction [2] has been described. IBD-IBS prevalence coincided within the disease subtypes. IBD-IBS diagnosis was linked to higher levels of narcotic use compared with those without, ulcerative colitis/indeterminate colitis, lower Quality of Life (QoL), anxiety, depression, fatigue, sleep disturbances, pain interference, and reduced social satisfaction.

The therapeutic approach of probiotics for targeting the gut microbiota in IBD-IBS has been recommended as a possible strategy [3-6]. Thus, probiotic therapies are emerging as a safe and natural strategy for the prevention and treatment of allergy and inflammation [7-8]. Earlier, it was suggested that selective and specified probiotic strains may advance potentially useful properties not least pertaining to anti-inflammatory effects, improvement of mucosal barrier homeostasis, beneficial effects on intestinal microbiota, and a decrease of visceral hypersensitivity [9]. Furthermore, Probiotics, as for example *Saccharomyces boulardii* and *Lactobacilli* (among which *Lactobacillus rhamnosus* is listed), synbiotics, prebiotics, psyllium, and some herbal medicinal products, primarily peppermint oil, have been shown to be effective in ameliorating IBS symptoms [10-13]. Curro et al., (2017) concluded that despite inconsistencies and lack of sufficient study-

design probiotics offered therapeutic options in the management of both FBD and IBD. Probiotics, following ingestion, produce microbial transformations in the gut-intestinal microbiota thereby exerting several health-promoting properties that include the maintenance of the gut barrier function and modulation of the host immune system [14-17]. The diversity of interactions between either microbiota or probiotics/prebiotics with various aspects of the immune system that promulgate to therapeutic applications for alimentary canal disorders offers an area of critical necessity for those afflicted, and novel therapeutic strategies are pursued diligently [18].

It has been observed that probiotics, defined as live microorganisms that may bestow health benefits to the host, have been investigated for diseases of the immune system, including allergies. They constitute living non-pathogenic microorganisms that may be administered to improve microbial balance, particularly in the gastrointestinal tract, often consisting of *Saccharomyces boulardii* yeast or lactic acid bacteria, such as *Lactobacillus* and *Bifidobacterium* species, and as such have been regulated as dietary supplements and foods. Probiotic yeast cells, prepared as suspensions, may be utilized as transporters of Extremely High Frequency (EHF) millimeter-wavelength, electromagnetic fields to induce and promote a range of neurobiologic and neuroimmunologic properties within different host organisms [19-21]. The millimeter-wavelength treated-yeast, Milmed, a probiotic intervention, with anti-neurodegenerative properties [22,23] was applied recently for the treatment of

recurrent seasonal and animal hair allergies over eight-week to twelve-week, twice weekly, administrations [24,25]. In a follow-up study [26] the effects of the patented treated-yeast, Milmed, a *Saccharomyces cerevisiae* species within a probiotic suspension, upon allergies presented by a group (n=8) of patients, that were compared with a matched group of patients administered untreated yeast cells, as a placebo control (n=8) confirmed the anti-allergic propensity. Treated yeast cells were subjected to the millimeter-wave exposure as outlined in the patented documents. Patients who had administered themselves the treated-yeast, Milmed, over periods extending from four-to-thirteen weeks, completed subjective self-report ratings of their allergy symptoms that indicated marked ameliorative effects; additionally, they rated their general health situations to be markedly improved. Those patients who had taken the untreated yeast did not report these improvements. Correlational analyses between the number of weeks treated Milmed was taken by patients and (i) the alleviation of allergy symptoms, and (ii) the improvement in general health status, indicated significant relationships in each case. The significant correlations between symptom improvements and general health status, on one hand, and the number of weeks treated Milmed was ingested imply that complete treatments are required for the optimal therapeutic benefits.

The purpose of the present study was to assess whether or not the Milmed probiotic may be efficacious for the amelioration of symptoms associated with the IBS-IBD condition. In vitro studies evaluating the

effects of incubating microglia and neuron-like cells with Milmed yeast upon exposure to the pro-inflammatory liposaccharide (LPS) showed that the treatment reinstated the recovery of the resting phenotype thereby implicating the anti-inflammatory propensity of the treated yeast [27]. In order to study in vivo the anti-inflammatory effects of Milmed upon the IBS-IBD condition the new preparation of the yeast in capsules that could be ingested was developed thereby both facilitating delivery and alleviating procedural difficulties. Each patient, whether receiving the Milmed yeast capsules or the untreated yeast capsules, ingested their respective preparation three times each week over twelve weeks.

Methods and materials

Participants

Twelve patients diagnosed with IBS/IBD with ages ranging from Patients' self-reports pertaining to symptoms reported for IBS/IBD. The patients included one male and eleven female patients assigned randomly to the Milmed (treated-yeast) and control (untreated yeast) groups. Their ages ranged from 25 to 79 years of age (mean $\pm$ SD=52.34 $\pm$ 17.29), Men ages: Milmed group=48.5 $\pm$ 13.1 years, Placebo group=56.2 $\pm$ 17.2 years. Each of the patients listed the symptoms that he/she had been afflicted with during the three months prior to participating in the study. The mean number of years that had elapsed following diagnosis were mean $\pm$ SD=10.46 $\pm$ 11.75 years. Patients administered three capsules/week to themselves. The final capsule was ingested either one, two or three weeks before completion of the questionnaire.

Treatment group assignment

Those patients who received treated yeast (Milmed, in capsules, 200 mg)

Patient 1

Female, aged 66, diagnosed with IBS for 5 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, nausea, flatulence, diarrhea, constipation, bloating (gas/fluid retention), heartburn (gastroesophageal reflux syndrome) and abdominal cramps.

Perceived improvement: reduced stomach pain and bloating.

Side effects: The patient reported no adverse side effects.

Patient 2

Female, aged 56, diagnosed with IBS for 10 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, nausea, flatulence, diarrhea, constipation, bloating (gas/fluid retention), heartburn, back-pain and abdominal cramps.

Perceived improvement: reduced intestinal problems, stomach pain and heartburn.

Side effects: The patient reported no adverse side effects.

Patient 3

Female, aged 65, diagnosed with IBS for 22 years.

Intake: 3 times a week before breakfast for 12 weeks.

Symptoms: Stomach pain, flatulence, diarrhea episodes, and bloating (gas/fluid retention).

Perceived improvement: reduced bloating.

Side effects: The patient reported no adverse side effects.

Patient 4

Female, aged 25, diagnosed with IBS for 4 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pains, nausea, flatulence, diarrhea episodes, bloating (gas/fluid retention) and heartburn (gastroesophageal reflux syndrome).

Perceived improvement: absence of stomach pains, abolished nausea, absence of heartburn and diarrhea episodes, reduced flatulence.

Side effects: The patient reported no adverse side effects.

Patient 5

Female, aged 28, diagnosed with IBS for 5 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, flatulence, diarrhea, constipation, bloating (gas/fluid retention) and abdominal cramps.

Perceived improvement faster recovery from relapses.

Side effects: The patient reported no adverse side effects.

Patient 6

Female, aged 51, diagnosed with IBS for 10 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach aches and pains, nausea, flatulence, constipation and bloating (gas/fluid retention).

Perceived improvement: reduced constipation and stomach pains.

Side effects: The patient reported no adverse side effects.

Placebo-group assignment: those patients who received non-treated yeast in capsules (200 mg)

Patient 7

Male, aged 79, diagnosed with IBS for 6 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, nausea, gas, diarrhea, bloating (gas/fluid retention) and heartburn (gastroesophageal reflux syndrome).

Perceived improvement: none reported.

Side effects: The patient reported no adverse side effects.

Patient 8

Woman, aged 50, diagnosed with IBD for 7 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, flatulence, diarrhea and bloating (gas/fluid retention) and indigestion.

Perceived improvement: none reported.

Side effects: The patient reported no adverse side effects.

Patient 9

Woman, aged 63, diagnosed with IBD for 42 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, nausea, flatulence, diarrhea episodes and bloating (gas/fluid retention).

Perceived improvement: none reported.

Side effects: The patient reported no adverse side effects.

Patient 10

Woman, aged 70, diagnosed with IBD for 2 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Diarrhea episodes, flatulence.

Perceived improvement: reduced flatulence.

Side effects: The patient reported no adverse side effects.

Patient 11

Woman, aged 39, diagnosed with IBD for 4 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, indigestion, diarrhea episodes, abdominal cramps and bloating (gas/fluid retention).

Perceived improvement: none.

Side effects: The patient reported no adverse side effects of treatment.

Patient 12

Woman, aged 36, diagnosed with IBD for 8 years.

Intake: 3 times a week before breakfast for 12 weeks

Symptoms: Stomach pain, gas, diarrhea, heartburn (gastroesophageal reflux syndrome), abdominal cramps and bloating (gas/fluid retention).

Perceived improvement: none reported.

Side effects: The patient reported no adverse side effects of treatment.

Quantification of symptoms

The patients each reported one or more of the following symptoms:

Stomach pain, nausea, gas, diarrhea episodes, constipation, bloating (gas/fluid retention), heartburn, abdominal cramps, back-pain, and indigestion. In each case, each symptom was awarded a value of 1 such that, for example in the case of Patient 1 the report of “Stomach pain, nausea, flatulence, diarrhea, constipation, bloating (gas/fluid retention), heartburn and cramps”, would quantify to 8 from the number of symptoms reported. Following calculation of number of symptoms

for each Milmed-treated and untreated yeast-treated patient, a priori t-testing, means and standard deviations were obtained.

Results

Twelve weeks intake of Milmed induced a significant reduction in the number of symptoms reported by the Milmed group in comparison with the control (placebo) group. Two-tailed tests indicated a significantly lower numbers of symptoms reported after the 12-week Milmed treatment whereas

before the treatment there was no difference the groups despite the number of reported symptoms being somewhat higher in the Milmed group. Table 1 presents the “number of reported symptoms” by patients administered either Milmed or Placebo (untreated yeast) for twelve weeks (3 times/week) and tested for self-report before and after the treatments (below). T-testing indicated a significant fewer number of symptoms by the group receiving Milmed than by the placebo group, following intervention.

Groups		Before	After
Number of reported symptoms			
Milmed	N=6	7.50 ± 2.88 ^{ns}	1.30 ± 0.84 ^{*, ∞}
Control ¹	N=6	4.50 ± 2.59	4.50 ± 2.49
*t=2.912, df=10, p=0.016.			
∞t=2.961, df=10, p=0.13.			
Pearson correlational analysis: Before and After			
R=0.143, t=0.658, df=12, non-significant			

Table 1: Number of reported symptoms by patients administered either Milmed or Placebo (untreated yeast) for twelve weeks and tested for self-report before and after the treatment.

*p=0.016, two-tailed t-test, versus control group

∞p=0.013, two-tailed t-test, versus Before
ns=not significant versus control group

¹Placebo=untreated-yeast

Correlational analysis with Pearson’s test indicated that there was no significant correlation between the Before and After reports of the patients’ symptoms.

Discussion

The findings of the present study design to assess the possible therapeutic effects of Milmed upon the symptoms associated with IBS-IBD were as follows: (I) Compared to the

placebo (administered untreated-yeast) control the Milmed group reported fewer symptoms, following treatment, and also fewer symptoms compared to the pre-treatment (before) report (see Table 1). (ii) There was no correlation between patients’ responses regarding symptoms Before and After intervention, possibly implying that both Milmed and the untreated-yeast placebo induced differential responses among the patient group. It ought to be noted that the treated-yeast, Milmed, nor the untreated-yeast placebo induced any adverse side effects among the patients in keeping with in vitro toxicology analysis and previous studies. Unpublished observations of several other patient-groups ingesting Milmed have shown

the administered dosage from 3/week capsules 1 daily, or even 2 daily, enhanced the therapeutic effects markedly. These findings of an in vivo anti-inflammatory effect confirm the previous in vitro report that milmed yeast does not produce any cytotoxic effects upon microglial cells nor upon cells of neuronal origin wherein there were indications neurotrophic activity [27].

The in vitro, cell culture study demonstrating anti-inflammatory effects of Milmed to block the LPS-induced inflammation of glial and neuronal cell-lines (manuscript in preparation), taken together with several other observations (manuscript in preparation), seem to be confirmed by the present study upon patients presenting IBS-IBD. Further confirmation appears to arise from studies carried out to test the efficacy of Milmed in facilitating the alleviation of physiologic health problems, mainly 'common-cold' and inflammation symptoms, performance improvements among racehorses in training [28]. In the first Study (n=8), "Time to reduce the horses' pulse to 130, immediately after strenuous exercise, and Pulse rate after 15-mins were estimated both before and after the Milmed treatment whereas in the second Study (n=15), the levels of improvement on a scale of 1-to-10, as well as on judgements of vigour, general health and performance following several weeks of Milmed administration to the horses in training were assessed. The first study indicated that those racehorses who had presented poor health (and were therewith selected for the Milmed treatment) evidenced improved physiologic health responses, as measured by "Time to reduce pulse levels to

130" and "Pulse rate after 15-mins", following Milmed treatment over several weeks; additionally, before-to-after Milmed treatment correlations were significant and positive for both the "Time taken to reduce pulse to 130" and "pulse rate after 15 min". The second study indicated that Milmed-treated racehorses in training showed improvements in both subjective health assessment and performance. Unfortunately, none of the horse-trainers involved in these studies would allow any of their animals to receive untreated-yeast to present a control condition. Nevertheless, these studies did provide in vivo indications of the utility of several weeks of the probiotic, Milmed, yeast treatment for the alleviation of mainly respiratory conditions among racehorses under the relatively stressful training and racing season thereby offering a suitable nutraceutical agent to alleviate inflammation in large animals.

Probiotics, including bacteria and yeast, live microorganisms that have demonstrated beneficial effects on health and performance have applications as adjuvant treatments for various gut-intestinal conditions [29]. In a study undertaken to ascertain the role of the probiotic, *Lactobacillus plantarum* strain JDFM LP11, a dietary bacterial food supplement, in the gut microbiota as a modulator of the immune gut-intestinal response in weaned piglets, it was observed that *L. plantarum* JDFM LP11, a particular strain of *Lactobacillus plantarum*, increased the population of lactic acid bacteria in faeces and enhanced the proliferation of villi in the small intestine [30]. Furthermore, both preclinical and clinical studies have shown

that probiotics may alter the intestinal microbiota through the promotion of potential control of multiple bowel disorders and induction of overall health and wellness [31]. In this regard, probiotic species, such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*, with species-, dose-, and disease-specific, and the duration of therapy action dependent on the clinical indication, are effective for acute infectious diarrhea, antibiotic-associated diarrhea, *Clostridium difficile*-associated diarrhea, hepatic encephalopathy, ulcerative colitis, irritable bowel syndrome, functional gastrointestinal disorders, and necrotizing enterocolitis [32]. Finally, the ongoing formulation of “microbiota-gut-brain axis” in gut-intestinal syndromes has described a role for the emerging probiotics modulating the integrity of the alimentary canal [33].

Conclusion

The Milmed group reported fewer symptoms, following treatment, compared with the placebo (administered untreated-yeast) control; they expressed also fewer symptoms compared with their pre-treatment questionnaire report. Untreated-yeast administration to patients did not induce any reduction of IBS-IBD symptoms. There was no significant correlation between patients’

reports before and after treatment. Neither Milmed nor untreated-yeast induced any adverse effects.

Limitations

Certain aspects of the instrument (questionnaire) applied in the present study dictate improvement despite the positive and encouraging results of Milmed therapy: (a) only six patients in each group were available for statistical analysis implying that power was unusually low possibly due to (b), (b) the questionnaire was found to comprise too many inadequacies, such as linguistic ambiguity of items, insufficiency of formulations and lack of structure which resulted in several incomplete responses and/or wrongly completed responses, and (c) patients would have benefitted from a longer intervention, e.g. 15 or 16 weeks, and more Milmed capsules ingested per week, e.g. once daily.

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