

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2019.08.818

Journal of GHR 2019 August 21; **8(4)**: 2919-2922
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

ORIGINAL ARTICLE

Treatment of Irritable Bowel Syndrome with *Saccharomyces Cerevisiae*

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Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: February 7, 2019

Revised: April 10, 2019

Accepted: April 16, 2019

Published online: August 21, 2019

ABSTRACT

AIM: To evaluate the effect of probiotic *Saccharomyces Cerevisiae* in the treatment of Irritable Bowel Syndrome in a randomized, double-blind placebo-controlled clinical trial.

METHODS: A randomized, double-blind placebo-controlled clinical trial has been performed in 347 adults, diagnosed with IBS (Rome III criteria). Subjects were randomized to receive 1000 mg BID of *Saccharomyces Cerevisiae* daily for four-week, product 177, placebo 170. IBS symptoms (abdominal pain/discomfort, bloating/distension, bowel movement difficulty) and changes in stool frequency and consistency were recorded daily by the patients and assessed weekly by the investigator.

RESULT: Improvement of Gastrointestinal symptoms was significantly higher in the product group, compared to the placebo, on (abdominal pain/discomfort, bloating/distension, bowel

movement difficulty, with stool modification), p -value < 0.001 in the treated group, and the ratio between groups (130 vs. 47), (73.4% vs. 27.64%).

CONCLUSION: *Saccharomyces Cerevisiae* significantly improves irritable bowel syndrome symptoms and is well tolerated.

Key words: Irritable Bowel syndrome; Abdominal pain; Probiotic *Saccharomyces cerevisiae*; Yeast

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Al Helo A. Treatment of Irritable Bowel Syndrome with *Saccharomyces Cerevisiae*. *Journal of Gastroenterology and Hepatology Research* 2019; **8(4)**: 2919-2922 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2510>

Abbreviations

IBS: Irritable Bowel Syndrome;

IBS-C: Irritable Bowel Syndrome with constipation predominant;

IBS-D: Irritable Bowel Syndrome with diarrhea predominant;

IBS-M: Irritable Bowel Syndrome Mixed;

RCT: Randomized Controlled Trial;

PPI: Proton Pump Inhibitor;

SPSS: Statistical Package for the Social Sciences.

INTRODUCTION

This study to evaluate the effect of probiotic *Saccharomyces Cerevisiae* in the treatment of Irritable Bowel Syndrome in a randomized, double-blind placebo-controlled clinical trial.

IBS is the most common functional gastrointestinal disorder, IBS is characterized by chronic and recurrent abdominal pain or discomfort and altered bowel habits.

IBS has an estimated worldwide prevalence of 14% in women and 9% in men and usually occurs before age 50 years, IBS has been subtyped according to predominant bowel habit as^[1].

IBS with constipation, IBS with diarrhea, Mixed type, and Unclassified.

Rome III Criteria for IBS: The criteria for a diagnosis of Irritable Bowel Syndrome (IBS) requires that a person is experiencing chronic

abdominal pain or discomfort at least three days throughout the last three months, with an onset of symptoms of IBS at least six months prior. These symptoms must also show^[2].

Pain symptoms are improved with a bowel movement, and The onset of symptoms related to a change in the frequency of the stool, and The onset of symptoms related to a change in the appearance of the stool.

Many pathophysiological mechanisms have been explained IBS such as^[3]. Altered GI motility and visceral hypersensitivity and dysfunction of the brain-gut axis and intestinal inflammation disturbance of the intestinal microflora.

Most recent studies proved that Dysbiosis of the Intestinal Microflora is the most likely cause and play a main role in IBS.

Postinfectious associated IBS and small intestinal overgrowth associated IBS and antibiotic-associated IBS, all of them associated with altered intestinal microflora.

Many medications used to treat IBS has no great effect. On the other side, previous studies prove that probiotics have a good treatment effect. Added to that, it is encouraging to use probiotics as they are natural, has no side effects and cheap. Thus, I used probiotic yeast *Saccharomyces cerevisiae* in the treatment of IBS as it is resistant against gastric and bile salts and can be used with antibiotics.

Only Two clinical studies (RCT) have been conducted on *Saccharomyces cerevisiae*^[3,4]. And the daily dose used in both studies is 1000 mg daily.

Intestinal microflora: A human intestine contains 10^{14} bacterial cells, which are ten times higher than the number of human cells in our body. 70% of our body normal microflora in the colon, which contains bacteria, fungi, viruses^[5].

The number of bacteria increases from the stomach (10^1 to 10^3 bacteria/g) to the colon (10^{11} to 10^{12} bacteria/g)^[6].

The content of the small intestine mainly Gram positive and aerobic bacteria; the large intestine contains predominantly Gram-negative and anaerobic bacteria. 95% of the colon bacteria are anaerobes, the Bacteroides, and Firmicutes^[7].

Benefits of intestinal flora: Fermentation of undigested food, endogenous mucus producing short-chain fatty acids, which are nutrients to the colonic epithelial cells and conservation of energy, absorption of sodium chloride and water from the right colon, synthesis of vitamins K, control of epithelial cell proliferation, protection against the pathogens by a barrier effect and training of the immune system^[8].

There are intrinsic and extrinsic factors that prevent overgrowth of bacteria in the small intestine, **intrinsic factors** include: 1. Gastric acidity and bile, Peristaltic activity which prevents adherence of bacteria, Normal gut defense mechanisms, including the humoral and the cellular, Mucin production by intestinal mucosa, Gut antibacterial peptide, the ileocecal valve which prevents retrograde translocation of bacteria from the colon to the small intestine.

Extrinsic factors include food and drugs that modulating gut flora, such as antibiotics and PPIs and h2 blockers^[9].

Evidence of Bacterial Disturbance Causing IBS

Post-infectious IBS: After acute gastroenteritis infectious etiology, up to 30% of patients complain of gastrointestinal symptoms for a long time, which meets irritable bowel syndrome criteria.

Probiotics are effective in restoring the intestinal microflora in patients with post-infectious IBS^[10].

Small Intestinal Bacterial Overgrowth and IBS: “A study undertaken at Cedars-Sinai Medical Center used 448 subjects who were referred by their doctors for the detection of SIBO. Of 202 irritable bowel syndrome patients, 157 (78%) had overgrowth. Of these, 47 had follow-up testing. Twenty-five of 47 follow-up subjects had eradication of small intestinal bacterial overgrowth. A comparison of those that eradicated to those that failed to eradicate revealed an improvement in irritable bowel syndrome symptoms with diarrhea and abdominal pain being statistically significant after Bonferroni correction ($p < 0.05$). Furthermore, 48% of eradicated subjects no longer met Rome criteria ($\chi^2 = 12.0, p < 0.001$). No difference was seen if eradication was not successful^[3,11,15].”

Small intestinal bacterial overgrowth is associated with irritable bowel syndrome. Eradication of the overgrowth eliminates irritable bowel syndrome by study criteria in 48% of subjects”.

Antibiotics and IBS (Iatrogenic IBS): Antibiotics significantly alter gut microflora causing an imbalance of the intestinal microflora, for example, many antibiotics cause pseudomembranous colitis^[12]. This study proves that “**Antibiotics** is a risk factor for irritable bowel syndrome.

An internet-based web panel representative of the Danish background population was invited to participate in a survey regarding the epidemiology of IBS in 2010, 2011 and 2013. A questionnaire based on the Rome III criteria for IBS was answered at all three occasions. In 2013, a question regarding the use of antibiotics in the past year was included.

Results

In 2013, the use of antibiotics was reported by 22.4% (624/2781) of the population. A higher proportion of individuals with IBS reported the use of antibiotics compared with asymptomatic controls [29.0% (155/534) vs. 17.9% (212/1,184), $p < 0.01$]. For asymptomatic respondents in 2010 and 2011 ($n = 1004$), the relative risk of IBS in 2013 related to the use of antibiotics was 1.9 [95% confidence interval (CI): 1.1-3.1]. Adjusting for sex by logistic regression, the use of antibiotics predicted the development of IBS with an odds ratio of 1.8 (95% CI: 1.0-3.2).

Antibiotics are a risk factor for IBS in asymptomatic individuals. Possible mechanisms should be investigated in future studies^[13].

Probiotics

The World Health Organization defines probiotics as “*live microorganisms, which, when taken in adequate amounts, confer a health benefit on the host,*” Probiotics can be bacteria, viruses, parasites, or yeasts.

Probiotics benefit to the body by various mechanisms: Pathogen suppression or Improvement of barrier function or Immunomodulation, or Neurotransmitter production^[14].

The strain of *Saccharomyces cerevisiae* CNCM I-3856 secretes saccharolytic enzymes and assists intestinal flora in the production of short-chain fatty acids that accelerate bowel movement. It also acts as a strong visceral analgesic, increasing resistance to pain by up to 40%. Additionally, it also acts as an intestinal anti-inflammatory factor^[14,11].

Probiotic balances the intestinal microflora composition as it reduces the harmful bacteria such as *Enterococcus spp.*, *Escherichia coli*, and *Candida albicans*. The result is an improvement of inflammation, bloating, pain, discomfort, constipation, all of which are symptoms of IBS^[15].

MATERIALS AND METHODS

Patients

Patients were selected in two investigative sites in Jordan, Jordanian Ministry of Health, and Saudi Arabia, Riyadh National Hospital from 1/09/2010 to 1/07/2015. Patients included in the study were males and females and the age between 18 and 70, diagnosed with IBS according to the Rome III criteria.

A pain/discomfort scored from 0 to 7.

Patients had normal blood counts, complete blood count, liver function test, renal function, thyroid function, before participating in the study.

Subjects were excluded if they had organic intestinal diseases, underwent treatments that influence is, or taking any medication or herbals or probiotics.

Study design

This is a 4-week double-blind placebo-controlled clinical study randomizing two parallel groups of IBS patients 177 experimental and 170 placebos, during a four-week period, scores of abdominal pain/discomforts, bloating and flatulence, defecation difficulty, stool frequency, and stool consistency were recorded.

Recommendations about diet were explained to all patients, after verification of the inclusion criteria, eligible IBS patients were randomized to consume daily for four weeks two tablets of cerevisiae CNCM I-3856 (1000 mg) with a meal and placebo (calcium gluconate 500 mg). Patients observed weekly by observer and provided consent before the inclusion of the study.

Study products and compliance evaluation

The products study was presented All in tablets of active product, and placebo was without flavour and had the same size, color. To be taken orally, two tablets a day with the launch and dinner time with a big glass of water. The probiotic preparation specifically 1000mg per tablet of *S. cerevisiae* CNCM I-3856, and the placebo consisted of calcium gluconate 500 mg.

Assessment of symptoms and study endpoints

Irritable bowel symptoms evaluated daily by patients and assessed each week during the 4-week study, according to a 7-point Likert scale.

Abdominal pain/discomfort scores analyzed, where the score at the week (W0) to (w4).

Secondary outcome measures were the weekly scores of bloating and or distension and bowel movement difficulty, recorded daily in the same condition using the 7-point Likert scales Changes in stool frequency and consistency were followed daily using the Bristol Stool Scale from (1) to (7)^[16].

Safety variables

Adverse events were recorded by patients and immediately transmitted to the investigator to estimate their severity.

Randomization and statistical methods

Statistical analyses were conducted using SPSS software.

Each person included in the visit (V1) randomly received one of the two products (placebo or active).

The block of statistical method was performed by type of subject (with predominant constipation) (IBS-C), with predominant diarrhea (IBS-D), or mixed symptoms (IBS-M)).

The AUCs (W1-W4) of the abdominal pain/discomfort scores,

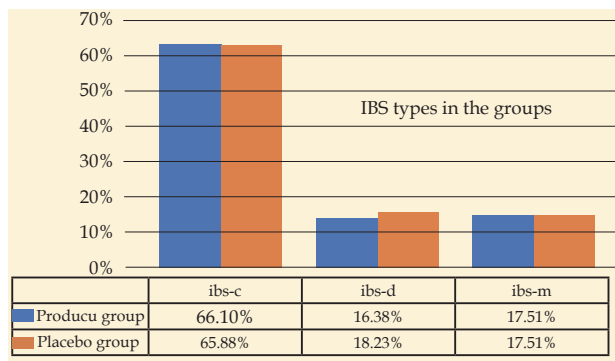


Figure 1 IBS types in the product and placebo groups.

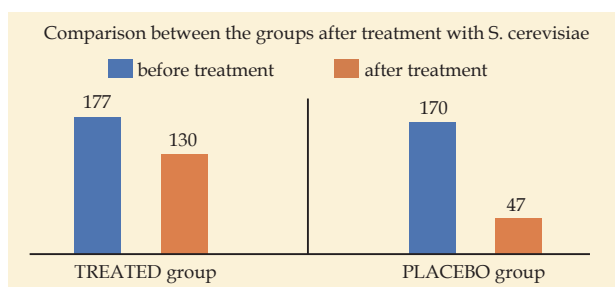


Figure 2 Comparison between groups after treatment.

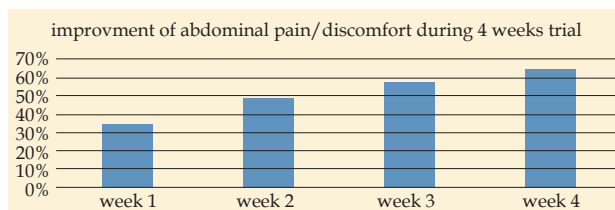


Figure 3 Improvement of abdominal pain/discomfort during the 4-week trial.

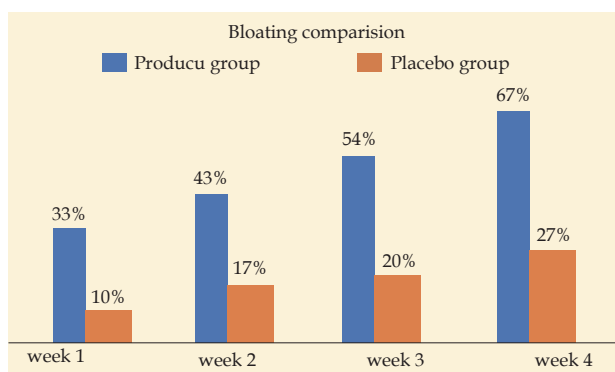


Figure 4 Comparison of bloating between groups.

bloating/distension scores, and bowel movement difficulty scores were calculated and analyzed^[17].

RESULTS

Primary outcome measures

Abdominal pain/discomfort scores, in AU on a scale from Zero (no symptoms) to Seven (severe symptoms), group analysis shows a significant reduction of the score in the probiotic groups throughout the 4 weeks of the treatment period (W0-4); this led to a mean score reduction of (130 vs. 47), (73.4% vs. 27.64%), in the experimental group and the p-value ($p < 0.001$).

DISCUSSION

This randomized controlled trial demonstrates in Jordanian and Saudi patients, based on two previous RCT trials evaluating the benefit of *Saccharomyces Cerevisiae* on Irritable Bowel Syndrome symptoms.

This probiotic was experimented on rats and showed a significant result in reducing pain. Other studies used other probiotics as lactobacilli or Bifidobacterial did not show a significant improvement in compared with *Saccharomyces cerevisiae* which plays an important role in improving IBS, as it is antibiotic resistant, and has a higher natural resistance against gastric acidity and bile salts^[18].

We treated 177 patients with probiotic yeast *S. Cerevisiae* with a dose of 1000 mg bid with a meal daily. A previous two studies treated subjects with 500 mg bid daily, and the placebo group (170 patients) were given calcium gluconate 500 mg daily for four weeks. And the results, including abdominal pain or discomfort, bloating and Bowel movement, stool consistency, were recorded daily by the patients and assessed every week by the investigator.

After 4 weeks of treatment, results show that there is an improvement of irritable bowel syndrome symptoms, including abdominal pain or discomfort, abdominal bloating, and stool consistency.

After the first week of the study abdominal pain in the treatment group significantly decreased, a score of 1 was 40 percent in the first week, and in the second week was 54 percent, and in the third week was 63 percent, and in the fourth-week score of 1 was 70 percent.

RCT conducted in IBS patients reported a mean response rate of 73.4% in a product group and 27.64% in the placebo group, (130 patients versus 47)^[19].

CONCLUSION

In conclusion, *S. cerevisiae* CNCM I-3856 at 2000 mg/day, conveniently delivered bid by two tablets 1000 mg, is well tolerated and improves irritable bowel syndrome symptoms. Further clinical studies are important to prove that *S. cerevisiae* improves IBS symptoms^[11].

Recommendation

Irritable bowel syndrome is a common gastrointestinal disorder, and the main cause of IBS is not yet clearly known. And many patients suffering from it and it is difficult to treat. This research focuses on probiotic *S. cerevisiae* which is natural and cheap with a very good result. We hope that in the future will be more studies about probiotics.

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