

1 A Randomized Clinical Trial of *Saccharomyces Cerevisiae* versus
2 Placebo in the Irritable Bowel Syndrome

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5

6 **Abstract**

7 Background: We aimed to evaluate clinical symptoms in subjects with irritable bowel
8 syndrome receiving *Saccharomyces cerevisiae* in a randomized double-blind placebo-controlled
9 clinical trial. Methods: 347 adults with irritable bowel syndrome (Rome III criteria) were
10 randomized to receive twice daily 1000 mg of *Saccharomyces cerevisiae*, delivered by two
11 tablets for four-week n=177 age: 35 ± 15, or placebo n=170 age: 35 ± 15 for 4 weeks. Result:
12 The proportion of responders, defined by an improvement of I.b.s symptoms (abdominal pain/
13 discomfort, bloating/distension, bowel movement difficulty) and changes in stool, was
14 significantly higher (p value < 0.001) in the treated group than the placebo group (130 vs 47),
15 (73.4

16

17 **Index terms**— abdominal pain, irritable bowel syndrome, probiotic *saccharomyces cerevisiae*, yeast.

18 **1 Introduction**

19 Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder. IBS is characterized by
20 chronic and/or recurrent abdominal pain or discomfort and altered bowel habits.

21 IBS has an estimated worldwide prevalence of 14% in women and 9% in men, and usually occurs before age
22 50 years.

23 IBS has been sub typed according to predominant bowel habit as:

24 ? IBS with constipation.

25 ? IBS with diarrhea.

26 ? Mixed type.

27 ? Unclassified.

28 **2 a) Rome III Criteria for IBS**

29 The criteria for a diagnosis of Irritable Bowel Syndrome (IBS) requires that a person be experiencing chronic
30 abdominal pain or discomfort at least three days over the course of the last three months, with an onset of
31 symptoms at least six months prior. These symptoms must also show:

32 ? Pain symptoms are improved with a bowel movement. ? Symptom onset is related to a change in the
33 frequency of stool. ? Symptom onset is related to a change in the appearance of stool.

34 Numerous pathophysiological mechanisms have been explained IBS, but the contribution of the gastrointestinal
35 microbiota and variations in its composition and function have only recently begun to be evaluated as a significant
36 component in the pathogenesis and pathophysiology of irritable bowel syndrome.

37 **3 b) Intestinal microflora**

38 Human intestine contains 10¹⁴ bacterial cells, which are 10 times higher than the number of cells in the human
39 body. Seventy percent of our body normal microflora in the colon, which contains bacteria, fungi, viruses.

40 The number of bacteria increases from stomach (10¹ to 10³ bacteria/g) to the colon (10¹¹ to 10¹² bacteria/g).

41 The small intestine contains mainly Gramm positive and aerobic bacteria, the large intestine contains
42 predominantly Gram negative and anaerobic bacteria. 95% of intestinal bacteria are anaerobes, Bacteroidetes
43 and Firmicutes.

44 **4 c) Benefits of intestinal flora**

45 Fermentation of undigested food, endogenous mucus producing short chain fatty acids, which are nutrients to the
46 colonic epithelial cells and conservation of energy, absorption of NaCl and water, from the right colon, synthesis
47 of vitamin K, control of epithelial cell proliferation, protection against pathogens by a barrier effect and training
48 of the immune system.

49 Intrinsic and extrinsic factors that prevent overgrowth of bacteria in the small intestine, intrinsic factors
50 include:

- 51 1. Gastric juice and bile. 2. Peristaltic movement which prevent adherence of bacteria.
- 52 3. Normal gut defense including humoral and cellular mechanisms. 4. Mucin production by intestinal mucosa.
- 53 5. Gut antibacterial peptide. 6. Ileocecal valve preventing retrograde translocation of bacteria from colon to the
54 small intestine.

55 Extrinsic factors include diet and drugs modulating gut flora, such as antibiotics and ppis and h2 blockers.

56 **5 d) Evidences of Bacterial Disturbance Causing IBS i. Post-
57 infectious IBS**

58 After acute gastroenteritis infectious etiology, up to 30% of patients complain of gastrointestinal symptoms for a
59 long time, which meet irritable bowel syndrome criteria.

60 Probiotics is effective in restoring the intestinal microbiota in patients with post infectious irritable bowel
61 syndrome.

62 **6 ii. Small Intestinal Bacterial Overgrowth and IBS**

63 A study undertaken at Cedars-Sinai Medical Center used 448 subjects who were referred by their doctors for
64 detection of SIBO. After completing a questionnaire, the researchers determined that 202 subjects could be
65 considered as having irritable bowel

66 The subjects' doctors then prescribed a 10-day course of antibiotics (e.g. Neomycin, ciprofloxacin, flagyl, or
67 doxycycline) to eradicate their bacterial overgrowth. Of the 157 initially qualifying subjects, 47 were referred back
68 by their doctors for a follow-up LHBT and were given a second questionnaire without being given the results
69 of their LHBT. Of these 47 subjects, 25 achieved complete eradication, and 22 incomplete eradication of their
70 SIBO. Antibiotic treatment significantly reduced hydrogen production in all 47 subjects, with greater reduction
71 in hydrogen production seen in those subjects whose SIBO was completely eradicated.

72 **7 iii. Antibiotics and IBS (Iatrogenic IBS)**

73 Antibiotics significantly alter gut microflora causing imbalance of the intestinal microflora, for example many
74 antibiotics causes pseudomembranous colitis.

75 A risk factor for irritable bowel syndrome in a population-based cohort Krogsgaard LR1, Engsbro AL2, Bytzer
76 P1, 3.

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

81 **8 e) Results**

82 In 2013, use of antibiotics was reported by 22.4% (624/2781) of the population. A higher proportion of
83 individuals with IBS reported use of antibiotics compared with asymptomatic controls [29.0% (155/534) vs.
84 17.9% (212/1,184), $p < .01$]. For asymptomatic respondents in 2010 and 2011 ($n = 1004$), the relative risk of
85 IBS in 2013 related with use of antibiotics was 1.9 [95% confidence interval (CI): 1.1-3.1]. Adjusting for sex by
86 logistic regression, development of IBS was predicted by use of antibiotics with an odds ratio of 1.8 (95% CI:
87 1.0-3.2).

88 **9 f) Conclusions**

89 Antibiotics is a risk factor for IBS in asymptomatic individuals. Possible mechanisms should be investigated in
90 future studies.

91 **10 g) Probiotics**

92 The World Health Organization define probiotics as "live microorganisms, which when taken in adequate amounts,
93 confer a health benefit on the host", Probiotics can be bacteria, virus, parasites, or yeasts.

94 Probiotics benefit to the body by various mechanisms: 1. Pathogen suppression 2. Improvement of barrier
95 function 3. Immunomodulation 4. Neurotransmitter production Strain of *Saccharomyces cerevisiae* CNCM
96 I-3856 secretes saccharolytic enzymes and assists intestinal flora by generating short-chain fatty acids that
97 accelerate bowel movement. It also acts as a visceral analgesic, increasing resistance to pain by up to 40 percent.

98 Additionally, it also acts as an anti-inflammatory to combat intestinal inflammation. To top it all off, the probiotic
99 rebalances microbial composition in the gut as it has been shown to reduce harmful bacteria such as *Enterococcus*
100 spp., *Escherichia coli* and *Candida albicans*. The result is decreased inflammation, bloating, pain, discomfort,
101 constipation all of which are symptoms of IBS.

102 **11 II.**

103 **12 Materials and Methods**

104 **13 a) Patients**

105 Patients were selected in two investigative sites in Jordan, Jordanian Ministry of Health, and Saudi Arabia,
106 Riyadh National Hospital from 1/09/2010 to 1/07/2015. Patients involved in the study were males and females
107 between 18 and 75 years of age with a diagnosis of IBS according to the Rome III criteria.

108 A pain/ discomfort score strictly above 1 and strictly below 6, as determined on a pain/discomfort scale using
109 arbitrary grading from 0 to 7.

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

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

114 **14 Figure 1 b) Study design**

115 This is 4-week double-blind placebo-controlled clinical study randomizing two parallel group of IbS patients 177
116 experimental and 170 placebos, During a four week period, scores for abdominal pain/discomfort (defined as a
117 non-comfortable sensation corresponding to a continuum between discomfort and pain), bloating And flatulence,
118 difficulty with defecation, stool frequency, and consistency were recorded.

119 Dietary recommendations were explained to each patient, After verification of the inclusion/exclusion criteria,
120 eligible IBS patients were randomized to consume daily, for 4 weeks, two tablets of *s.cerevisiae* CNCM I-3856
121 (1000 mg) with meal and placebo (calcium gluconate 500 mg). Patients were followed weekly and provided
122 consent before inclusion in the study.

123 **15 c) Study products and compliance evaluation**

124 The products studied were presented in all tablets of active product and placebo was without flavour, and had
125 the same size, colour. They were to be taken orally, two tablets a day with launch and dinner time with a glass of
126 water. The probiotic preparation specifically 1000mg per tablet of *S. cerevisiae* CNCM I-3856, and the placebo
127 consisted of calcium gluconate 500 mg.

128 **16 d) Assessment of symptoms and study endpoints**

129 Ibs symptoms evaluated daily and assessed each week during the 4-week study according to a 7-point Likert scale.
130 Abdominal pain/discomfort scores were first analyzed, where the score at week 0 (W0) to (w4).

131 Secondary outcome measures were the weekly scores of bloating/distension and bowel movement difficulty,
132 recorded daily in the same condition using the 7-point Likert scales Changes in stool frequency and consistency
133 were followed daily using the Bristol Stool Scale (ranging from 1, corresponding to separate hard lumps, to 7 for
134 entirely liquid stools).

135 **17 Figure 2 e) Safety variables**

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

138 **18 f) Randomization and statistical methods**

139 Randomization and statistical analyses were conducted using SPSS software.

140 Each subject included at the visit (V1) received in a random manner one of the two products (placebo or
141 active).

142 Block randomization was performed by type of subject (with predominant constipation) (IBS-C), with
143 predominant diarrhea (IBS-D), or mixed symptoms (IBS-M)) with dynamic allocation software using the block
144 permutation technique.

145 The AUCs (W1-W4) of the abdominal pain/discomfort scores, bloating/distension scores, and bowel movement
146 difficulty scores was calculated and analyzed.

147 19 III.

148 20 Results

149 21 a) Primary outcome measures

150 Abdominal pain/discomfort scores, expressed in AU on a scale from 0 (no symptoms) to 7 (severe symptoms),
151 Intra group analysis revealed a significant reduction of the score in the probiotic groups throughout the 4 weeks
152 of treatment period (W0-4); this led to a mean score reduction of (130 vs 47), (73.4% vs 27.64%) compared with
153 baseline, respectively in the product group ($p < 0.001$) in both treated groups.

154 IV.

155 22 Discussion

156 The present randomized double-blind placebocontrolled study demonstrates, in Jordanian population and Saudi
157 population, that *S. cerevisiae* CNCM I-3856 is safe and improves abdominal pain/discomfort. In IBS and other
158 patients fulfilling the Rome III criteria, the Based on these data and expecting a 45.76% therapeutic gain over
159 placebo for the score assessing abdominal pain/discomfort, 347 IBS patients were randomized and treated for 4
160 weeks with either *S. cerevisiae* CNCM I-3856 at a daily dose of 2000 mg 1000mg bid, or placebo 500 mg calcium
161 gluconate.

162 After the first week of the study abdominal pain in the treatment group significantly decreased, score of 1
163 was 40 percent at the first week, and at the second week was 54 percent, and at the third week was 63 percent,
164 and at the fourth week score of 1 was 70 percent. As a result, (abdominal pain/discomfort, bloating/distension,
165 bowel movement difficulty and changes in stool frequency and consistency) had improved, if we compare treated
166 group and the placebo group (130 vs 47), (73.4% vs 27.64%).

167 Probiotic administration is considered safe and acceptable strategy in IBS. Most studies evaluating the effects of
168 probiotics in IBS patients have been performed with bacterial strains of lactobacilli and/or bifidobacteria. Despite
169 the numerous advantages offered by yeast compared to bacteria, including antibiotic and phage resistances, as
170 well as higher natural resistance against gastric acid and bile salts, and stronger capacity to regulate the immune
171 response, only two clinical trials assessed the effect of yeast in patients with IBS. V.

172 23 Conclusion

173 In conclusion, *S. cerevisiae* CNCM I-3856 at 2000 mg/day, conveniently delivered bid by two tablets 1000 mg,
174 is well tolerated and reduces abdominal pain/discomfort scores with altering stool frequency and consistency.
175 Further clinical studies are warranted to confirm that *S. cerevisiae* could be a new promising candidate to
improve abdominal pain/digestive discomfort in subjects with IBS.

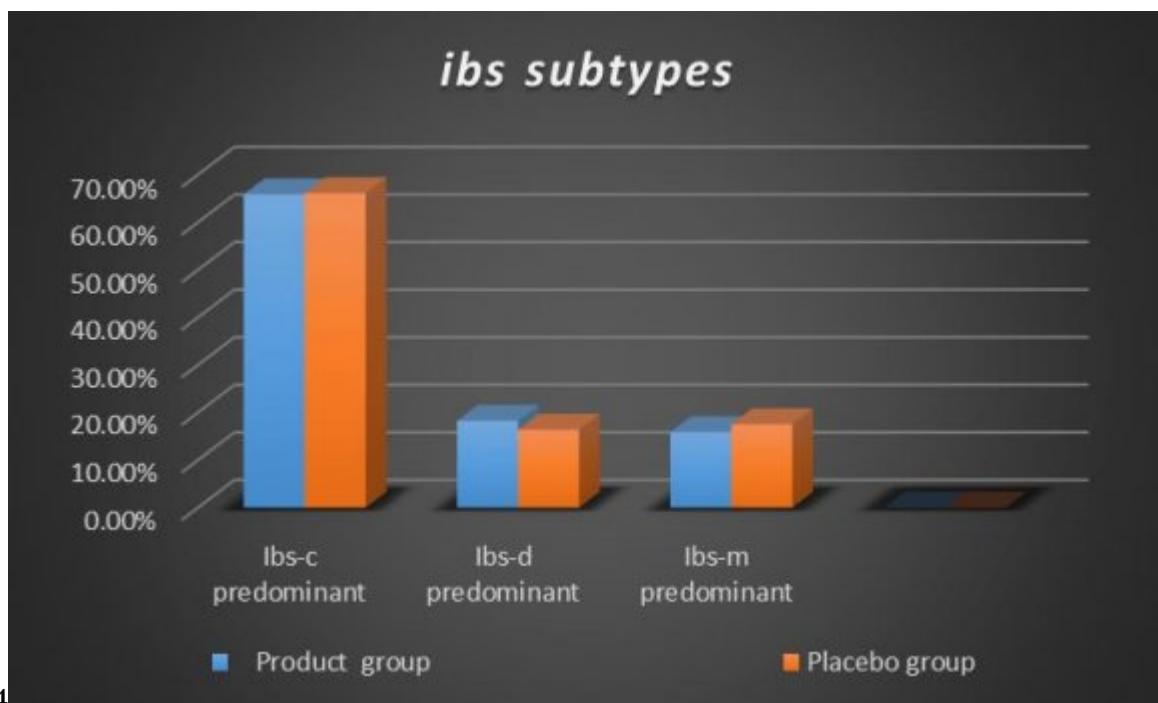


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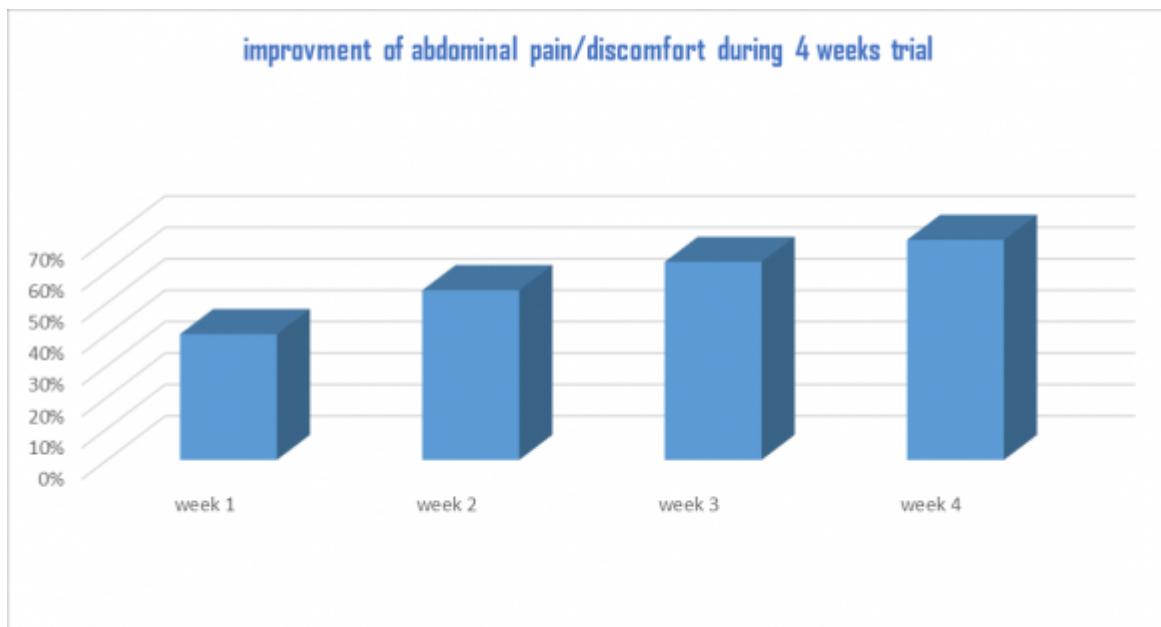


Figure 2:

177 [Probiotics] , Probiotics . <https://www.medicinenet.com/probiotics/article.htm>

178 [Guillaume Pineton De Chambrun ()] *A randomized clinical trial of saccharomyces cerevisiae versus placebo in*
179 *the irritable bowel syndrome*, Christel Guillaume Pineton De Chambrun . <https://www.ncbi.nlm.nih.gov/pubmed/25488056> 2015. p. .

180

181 [Sm ()] 'A role for the gut microbiota in ibs'. Collins Sm . <https://www.ncbi.nlm.nih.gov/pubmed/24751910> *Nature reviews gastroenterology & hepatology* 2014. 11 p. . (Article)

182

183 [a-z-digestive-topics/ibs-or-smallintestinal-bacterial-overgrowth 16 Saccharomyces Serevisiae (2017)] 'a-z-
184 digestive-topics/ibs-or-smallintestinal-bacterial-overgrowth 16'. <https://www.sciencedirect.com/topics/neuroscience/saccharomyces-cerevisiae-Saccharomyces-Serevisiae> 20/07/2017.
185 20/07/2017. (IBS or Small Intestinal Bacterial Overgrowth)

186

187 [Krogsgaard et al. ()] *Antibiotics: a risk factor for irritable bowel syndrome in a population-based cohort*, Lr1
188 Krogsgaard , Al2 Engsbro , P1 Bytzer . <https://www.ncbi.nlm.nih.gov/pubmed/30189148> 2013. 3.

189

190 [Pimentel et al. ()] *Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel*
191 *syndrome, Study*, M Pimentel , E J Chow , H Lin . <https://www.ncbi.nlm.nih.gov/pubmed/11151884>
192 2000.

193

194 [Yamada] *Irritable bowel syndrome, Textbook of gastroenterology*, Tadataka Yamada . p. . (volume set 5 th edition
195 by)

196 [Camilleri and Choi ()] 'Review article: irritable bowel syndrome'. M1 Camilleri , M Choi . <https://www.ncbi.nlm.nih.gov/pubmed/9042970> *Alimentary Pharmacology and therapeutics* 1997. 11 p. .

197

198 [Cayzeele-Decherf and Pélerin] *Saccharomyces cerevisiae. CNCM-3856 in irritable bowel syndrome: an individual subject meta*, Amélie Cayzeele-Decherf , Fanny Pélerin . <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5236513/> p. .

199

200 [Parkes et al. ()] *Symposium on dietary management of disease treating irritable bowel syndrome with probiotics: the evidence*, G C Parkes , . D Sanderson , K Whelan . <https://www.ncbi.nlm.nih.gov/pubmed/20236566> 2010. p. .

201

202 [Em and Ohman ()] 'The microbiota link to irritable bowel Syndrome: an emerging story Jeffery'. Quigley Em
203 , Ohman . <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3495796/> Article et al 2012. 3 p. .

204

205 [Harper et al.] 'The role of bacteria, probiotics and diet in irritable bowel syndrome'. Ashton Harper , M Aalwina
206 , Davinder Naghibi , Garcia . <https://www.ncbi.nlm.nih.gov/pubmed/29373532> Article 2018 p. .

207

208 [Treatment of irritable bowel syndrome in adults (2017)] *Treatment of irritable bowel syndrome in adults*, <http://www.dynamed.com> 19/07/2017. (Probiotics for irritable bowel syndrome)