

# The Effectiveness of Yogurt+ Probiotic on Chemotherapy-Related Diarrhea in Patients with Colorectal Cancer: A Randomized Clinical Trial

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## Abstract

**Background:** Chemotherapy-related diarrhea reduces patients' quality of life and sometimes changes or interrupts their treatment regimen. This study aimed to evaluate the effect of yogurt with probiotics on diarrhea caused by chemotherapy.

**Method:** The present study was a randomized controlled clinical trial. The sample consisted of 66 patients with colorectal cancer, recruited with convenience sampling method from patients who were referred to Buali Hospital of Tehran. The samples were randomly divided into three groups. The first group received yogurt with probiotics, the second group received yogurt alone, and the third group of control did not use yogurt during treatment. Data were gathered using the diarrhea section of adverse events. The number of defecations, the severity of diarrhea, and the consistency of stool in the seven days of the intervention were compared among the three groups. Analysis of variance and Tukey's post hoc test were performed through SPSS software.

**Results:** The number of defecations in the yogurt group with probiotics and yogurt was significantly lower than the control group ( $P < 0.05$ ). The severity of diarrhea in the yogurt group with probiotics decreased more rapidly ( $P < 0.05$ ). Stool consistency in the yogurt group with probiotics was significantly better than the control group ( $P < 0.05$ ).

**Conclusion:** Based on the results of the present study, yogurt with probiotics can reduce and improve diarrhea caused by chemotherapy. The results also showed that yogurt alone can reduce diarrhea and improve its symptoms.

**Keywords:** Probiotics, Yogurt, Diarrhea, Chemotherapy, Cancer

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## Introduction

Colorectal cancers are among the most prevalent cancers.<sup>1</sup> They are the second most common cancer in women and the third in men<sup>2</sup> and they are among the deadliest cancers in the world.<sup>3</sup> Most patients with this type of cancer are old.<sup>4</sup> Over 75% of patients with rectal cancer and 80% of patients with colon cancer are over 60 years old at the time of diagnosis.<sup>5</sup> The old age of patients with this cancer makes it difficult to tolerate some treatments and their side-effects.

Advances in technology and medicine have increased the chances of cancer patients' survival.<sup>6</sup> Current cancer treatments are surgery, radiation therapy, and systemic methods, such as chemotherapy, hormone therapy, immunotherapy, gene therapy, and targeted molecular therapies.<sup>7</sup> The side-effects of these treatments impact their effectiveness.<sup>8,9</sup> In addition to causing discomfort, some of the side-effects of cancer treatments can be life-threatening. Chemotherapy is a systemic treatment that affects various systems of the body, including the gastrointestinal tract. One of the most annoying complications of it is chemotherapy-related diarrhea.<sup>10</sup>

Chemotherapy-related diarrhea is one of the most common and complicating side-effects of chemotherapy, affecting more than 80% of patients receiving chemotherapy.<sup>11</sup> It is caused by gastrointestinal mucositis.<sup>12</sup> Mucositis is due to the direct or indirect effects of chemotherapy on gastrointestinal epithelial cells, which causes their apoptosis (cell death). Diarrhea can severely reduce patients' quality of life.<sup>13</sup> Severe diarrhea can also cause dehydration, malnutrition, and infection in patients with low white blood cells.<sup>14</sup>

Severe diarrhea can interrupt treatment or change the chemotherapy regimen.<sup>13</sup> It is reported that up to 80% of patients who were treated with chemotherapy regimens containing 5-fluorouracil and irinotecan experienced diarrhea which was severe in 3% of patients.<sup>15</sup> Severe diarrhea leads to a change in treatment in approximately 60% of patients, a reduction in the dose of drugs in 22%, a delay in receiving at least one dose in 28%, and a complete cessation of treatment in 15% of the patients. With early and effective

intervention, diarrhea and interruption of treatment can be prevented.<sup>16</sup> Therapies should be developed to reduce these complications and help to continue effective treatment.

Treatment for chemotherapy-related diarrhea (CRD) includes non-pharmacologic and pharmacologic interventions. Treatment aims to slow diarrhea and perform careful serial evaluation to assess response to therapy and to rule out significant volume depletion or other risk factors that would require hospitalization. It is recommended to classify patients with CRD as "uncomplicated" or "complicated". Patients with uncomplicated CRD have mild to moderate diarrhea, without severe abdominal cramping, nausea/vomiting, decreased performance status, fever, frank bleeding, or suspected dehydration. Initially, these patients can be managed conservatively at home with oral hydration, dietary modification, and antidiarrheal therapy (loperamide 4 mg followed by loperamide 2 mg every 4 hours). Patients with complicated CRD present with grade 3 or 4 diarrhea or they have grade 1 or 2 diarrhea with complications like severe cramping or vomiting. Patients with complicated CRD need aggressive management.<sup>17</sup>

In recent years, the use of probiotics for the prevention and treatment of diseases, such as necrotizing enterocolitis,<sup>18</sup> acute infectious diarrhea, and diarrhea caused by antibiotics, has become popular and has had beneficial results.<sup>19,20</sup> The human intestine contains hundreds of different species of bacteria. Bifidobacterium or Lactobacillus belong to the natural intestinal flora. Probiotics can improve the balance of intestinal microbes.<sup>21</sup> Due to the positive effect of probiotics in the treatment of infectious and non-infectious intestinal diseases, such as irritable bowel syndrome,<sup>22</sup> it seems that they can be a good candidate for the treatment of diarrhea caused by chemotherapy. The results of a case study demonstrated that probiotics are candidates for advanced breast cancer patients with CRD.<sup>23</sup> The results of the meta-analysis revealed that the application of probiotics before or during chemotherapy can prevent the occurrence of CRD effectively among cancer patients. They did not

**Table 1.** Comparison of sex and type of cancer in the study groups

Variable	Yogurt + probiotic	Yogurt	Control	Sum	Chi-square
<b>Gender</b>					
Female	13 (68.42 %)	14 (63.63 %)	18 (72 %)	45	Chi = 0.378, df = 2, P = 0.828
Male	6 (31.58 %)	8 (36.37 %)	7 (28 %)	21	
<b>Cancer place</b>					
Colon	14 (73/68 %)	14 (63.63 %)	16 (64 %)	44	Chi = 0.592, df = 2, P = 0.744
Rectum	5 (26.32 %)	8 (36.37 %)	9 (36 %)	22	

find the same results in the treatment of CRD.<sup>24</sup> The results of another meta-analysis showed that probiotics generally may have a beneficial effect in the prevention of CRD, especially for severe diarrhea, and may rarely cause adverse effects.<sup>25</sup> The results of these studies indicate that while there is no consensus on the efficacy of probiotics on the prevention of CRD, there were no agreements on their efficacy in the treatment of CRD.<sup>26, 27</sup>

The effectiveness of probiotics in the treatment of viral and bacterial diarrhea has been demonstrated. The results of some previous studies have also shown that probiotics have been effective in preventing CRD. However, several studies have not been able to confirm this effectiveness.<sup>24, 26</sup> Their efficacy on the treatment of CRD is not fully understood. Based on this gap in the knowledge, we decided to conduct the current study to determine the effectiveness of probiotic yogurt on CRD in patients with colorectal cancer.

## Subjects and Methods

### Study design and setting

The study was a placebo-controlled randomized clinical trial with three-arm parallel groups. 66 patients with colorectal cancer who underwent chemotherapy and reported CRD were randomly assigned to three groups, including yogurt + probiotics, yogurt, and control. The study population consisted of patients with colorectal cancer referred to Buali Hospital of Tehran affiliated with Tehran Islamic Azad University of Medical Sciences and Mehr Hospital of Tehran from December 2020 to September 2020 for chemotherapy.

### Sampling method

The participants were divided into three groups: yogurt and probiotic, yogurt, and control. The minimum sample size for each group was calculated to be 22 people using the formula for mean comparison, based on the following criteria standard deviation of the severity of diarrhea from the study of Mansouri et al.,<sup>28</sup>  $\sigma = 0.58$ ,  $\alpha = 0.05$ ,  $\beta = 0.8$ , and  $d = 0.67$ . Inclusion criteria were the patients aged between 18 to 65 with colorectal cancer, whose chemotherapy regime was 5-fluorouracil based on patients' weight, had CRD, did not have lactose intolerance, had no diarrhea before chemotherapy, and had the ability to eat and drink, with the performance status 0 or 1 based on Eastern Cooperative Oncology Group (ECOG). Exclusion criteria were unwillingness to continue participating in the study, being under or history of radiotherapy and targeted therapies, history of underlying diseases, such as inflammatory bowel disease (IBD) and previous history of total colectomy, possible complications after using yogurt or probiotics, change of treatment regimen, patients with IBD, or death of the patient. The study subjects were randomly allocated to yogurt + probiotic, yogurt, and control groups through Random Allocation Software (RAS) through random block sizes of six with an allocation ratio of 1:1. The person not participating in the research carried out random sequencing allocation. Containers were numbered from 1 to 90 according to the sequence generated. Recruitment and allocation to study groups are presented in figure 1.

### Intervention

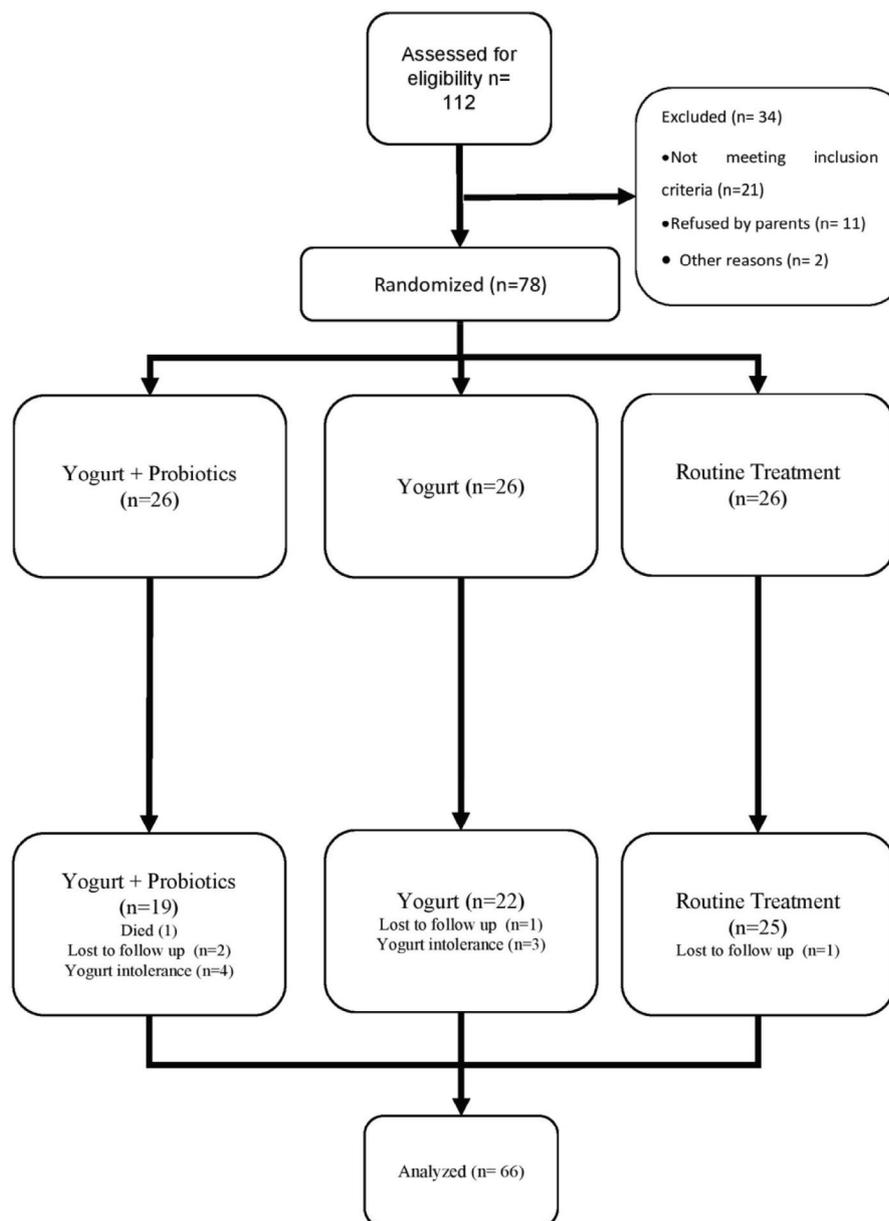
After explaining the study aims and procedures, written informed consent was obtained and the study subjects were assigned randomly. We applied the symptomatic treatment of diarrhea

conducted in all the groups (Loperamide 4mg followed by 2 mg every 4 hours). The intervention group received symptomatic treatment along with yogurt (150 Grams) and 1 probiotic capsule before breakfast and dinner twice a day for one week. The probiotic capsules contained 500 mg of lactobacillus casei, lactobacillus acidophilus, lactobacillus rhamnosus, lactobacillus bulgaricus, bifidobacterium breve, bifidobacterium longum, streptococcus thermophiles, and fructooligosaccharides as a prebiotic. The placebo group received symptomatic treatment with regular yogurt (150

Grams) before breakfast and dinner twice a day for one week. The controls received symptomatic treatment with no further intervention. The study subjects reported and documented defecation frequency, intensity, and stool form daily for one week.

### Measures

Herein, we assessed diarrhea frequency and intensity along with stool consistency as the three variables of the study. The study scale was a self-reported table developed by the research team.



**Figure 1.** The recruitment and allocation of study subjects to groups and follow-up are presented.

**Table 2.** The comparison of defecation number, severity of diarrhea, and stool consistency among the three groups in seven days of intervention

Factor	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<b>Defecation</b>							
Control	4.68	4.84b	4.80b	4.24a	3.92a	3.68b	2.80
Yogurt	4.36	4.41a	3.95ab	3.77ab	3.23ab	2.77a	2.05
Yogurt ± Probiotic	4.63	4.21a	3.63a	3.11b	2.74b	2.26a	2.16
<i>P</i> -value	0.315	0.042	0.001	0.008	0.010	0.001	0.154
<b>Severity of diarrhea</b>							
Control	1.48	1.68a	1.76a	1.16a	1.12a	1.08a	0.40
Yogurt	1.32	1.27ab	0.91b	0.86ab	0.64ab	0.41ab	0.32
Yogurt ± Probiotic	1.47	1.16b	0.74b	0.58b	0.37b	0.16b	0.21
<i>P</i> -value	0.521	0.021	0.001	0.049	0.007	0.009	0.545
<b>Stool consistency</b>							
Control	6.88	6.60	6.40	6.48a	6.32a	5.84	4.96
Yogurt	6.59	6.68	6.00	6.09ab	5.95ab	5.82	4.77
Yogurt ± Probiotic	6.47	6.26	6.21	5.58b	5.63b	5.32	4.89
<i>P</i> -value	0.011	0.040	0.159	0.003	0.005	0.053	0.941

It consisted of three main questions regarding the study variables. The validity of the scale was confirmed using the content validity method. Three oncologists confirmed the scale validity. The reliability of the scale was confirmed. Three main variables, including diarrhea frequency and intensity and stool consistency, were documented daily for one week after the start of the intervention based on the patient's report. The severity of diarrhea was assessed with the diarrhea section of adverse events. Based on this scale diarrhea has five grades. Grade 1 or mild is defined as an increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline. Grade 2 or moderate is an increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline. Grade 3 or severe is defined as an increase of  $\geq 7$  stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care. In grade 4, life-threatening consequences have happened and urgent intervention is indicated. Death is grade 5. The severity of CRD is described using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grades. Based on these criteria, severity is determined by the number of stools per day or an increase in ostomy output compared with baseline, the need for hospitalization and the effect on activities of self-care.<sup>17</sup>

### Statistical analysis

Data were analyzed via SPSS 16. Shapiro-Wilk test was used to find out the normality distribution of the data. One-way ANOVA with post hoc Tukey test was employed for statistical analysis for collecting data at a 95% confidence level ( $P < 0.05$ )

### Ethical considerations

The study protocol was approved by the Ethics Committee of Tehran Islamic Azad University of Medical Sciences (IR.IAU.TMU.REC.1399.147). The trial is registered on IRCT (IRCT20100911004728N4). Before participation in the study, written informed consent was obtained from each participant.

### Results

At the end of the study, we analyzed the results of the 66 samples in three groups: 19 in the yogurt and probiotic group, 22 in the yogurt group, and 25 in the control group. The mean  $\pm$  standard deviation (SD) of the age of the subjects was  $53.42 \pm 8.35$  in the yogurt + probiotic group,  $60.27 \pm 4.98$  in the yogurt group, and  $55.76 \pm 6.45$  in the control group. According to the results of table 1, most of the subjects in the three groups were women. Moreover, the number of patients with colon cancer in all the three groups was higher than the number of patients with rectal cancer. There were no significant differences in terms of gender and type of cancer between the

three groups ( $P < 0.05$ ). The ECOG scores revealed that most subjects were at level 0.

The comparison of the frequency, the severity of diarrhea, and stool consistency are presented in table 2. The comparison of the average number of defecations between the three groups shows that on the day 2 and 3, the average number of defecations in the yogurt + probiotic and yogurt groups was significantly lower than the average in the control group ( $P < 0.05$ ). On days 4 and 5, the yogurt + probiotic group has a significantly lower mean of defecation compared with to the control and yogurt group. On day 6, the controls had significantly higher defecation than yogurt and yogurt + probiotic subjects. On day 7, there were no significant differences in the mean defecation number among the three groups. The severity of diarrhea on day 1 was similar in the three groups. On days 2, 4, 5, and 6, the severity of diarrhea in the control group was higher than that of the subjects in the yogurt + probiotics ( $P < 0.05$ ). Stool consistency on days 4 and 5 was significantly better in the yogurt + probiotic group in comparison with controls. There were no significant differences between yogurt alone with yogurt + probiotics ( $P > 0.05$ ) in terms of stool consistency.

## Discussion

The results of the study illustrated that consumption of probiotic yogurt can significantly reduce CRD. The mean number of defecations reduced more quickly in those consuming yogurt and probiotics. Probiotics also had a positive effect on reducing the severity of diarrhea and improving stool consistency.

The results of previous studies have shown that the use of probiotics in CRD is safe. They can also reduce the incidence of diarrhea, if used before chemotherapy. In a meta-analysis, the results revealed that among 13 studies none had reported obvious adverse events. These results suggested that probiotics can safely and effectively help in the prevention of CRD. They concluded that probiotics are worthy of further research and promotion.<sup>23</sup> The results of a meta-analysis study on nine clinical trials in patients with abdominal

and pelvic cancer found that probiotics can be useful in preventing CRD and have no adverse effects.<sup>25</sup> The results of a more recent meta-analysis of 23 clinical trials stated that the use of probiotics before chemotherapy prevented the onset of CRD.<sup>29</sup>

The results of our paper were in line with those of previous studies. Based on previous researches, probiotics are safe and effective in the prevention of CRD. While previous studies have assessed the probiotics efficacy on the prevention of CRD, we examined the efficacy of them in the treatment of CRD. We did not find any studies assessing the effectiveness of the probiotics efficacy in the treatment of CRD. The effect of yogurt on the treatment of CRD was not also the title of research. Previous studies have illustrated that the incidence of grade  $\geq 3$  and  $\geq 2$  diarrhea was significantly reduced in the probiotics group.

Probiotics have been employed in a wide range of gastrointestinal disorders.<sup>24</sup> The reason for their effectiveness is their ability to maintain the stability of the intestinal microbiota.<sup>30</sup> Probiotics can tolerate the acidic environment of the stomach and reach the intestines. They can also produce butyric acid, stimulating the growth of intestinal epithelial cells.<sup>31</sup> Probiotics can also reduce intestinal inflammation,<sup>12, 32, 33</sup> which is effective in the studies on irritable bowel syndrome.<sup>21, 25</sup> Accordingly, probiotics can prevent and treat CRD through several mechanisms, including reducing the apoptosis of intestinal epithelial cells, repairing intestinal obstruction, improving intestinal flora, and reducing the production of inflammatory cytokines.<sup>34</sup> These factors promote epithelial cell repair, maintain intestinal homeostasis, and reduce intestinal inflammation.

Animal and clinical studies have demonstrated that the microbiota of the gut in patients receiving chemotherapy are markedly changed. For example, they found significant reductions in bifidobacteria, Clostridium group XIVa, and Clostridium genus along with increases in Enterobacter and Bacteroides. These changes can result in intestinal mucositis, lastly leading to diarrhea.<sup>35</sup> Normally, microbial diversity stabilizes the microecology of the gut. Chemotherapy

usually destroys microbial diversity.<sup>34</sup> It also increases the risk of the growth of pathogenic bacteria, such as *Escherichia coli*.<sup>36</sup> Mucositis is reduced with chemotherapy using probiotics. It also increases microbial diversity in the intestines.<sup>34</sup> Probiotics may prevent and treat CRD through several mechanisms. They modify the composition of intestinal microflora. They also form a protective physical barrier that can interfere with the attachment of pathogenic bacteria. They may also bind and reduce carcinogens. Another suggested effect is the exertion of trophic and anti-inflammatory substances affecting bowel mucosa. Probiotics also produce lactic acid which creates an acidic environment that is unfavorable for pathogens.<sup>37</sup> The following mechanisms of probiotics actions include stopping the adhesion and growth of harmful bacteria onto the gastrointestinal mucosa. They also enhance the mucosal barrier function of the gastrointestinal mucosa and repair the jejunal villus damage. Other proposed mechanisms are down-regulating the mRNA expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), and interleukin-1 $\beta$  (IL-1 $\beta$ ).<sup>24</sup> Through these mechanisms, probiotics can reduce the severity of diarrhea, abdominal discomfort, and intestinal toxicity.

Our results also demonstrated that yogurt alone can also reduce CRD. Yogurt has been shown to have good effects in the treatment of infectious and non-infectious diarrhea.<sup>20, 38</sup> The results of studies on other disorders, especially diarrhea in children, have revealed that yogurt alone can decrease diarrhea. Yogurt can reduce diarrhea by lowering intestinal inflammation, creating a suitable environment for the growth of beneficial bacteria while it has beneficial bacteria in it.<sup>39</sup> The results of the present study also shed light on the effectiveness of yogurt in reducing CRD; however, the effect of yogurt with probiotics was greater than that of yogurt alone.

The most important strength of the present study is its evaluation of the effect of probiotics on the treatment of CRD. Most previous studies have examined the safety and effectiveness of probiotics in preventing CRD. There were three

groups in this study and one group did not receive any complementary intervention. Compared to previous research, the effectiveness of probiotics against yogurt and the control group in the treatment of diarrhea was another strength of the current paper. The main weakness of the study was the small number of samples, which reduces the generalizability of the results. Another weakness of the study was that it did not examine other consequences of using probiotics, such as reduced bloating. We recommend that they be addressed in future studies.

### Limitations

The most important limitation of the present study was the lack of adequate control over the patients' diets since probiotics can enter the human diet from a variety of sources. We suggest that future studies have more control over patients' diets.

### Conclusion

According to the results of the present research, yogurt + probiotics can reduce and treat CRD. The results also showed that yogurt alone can decrease diarrhea and improve its symptoms. Based on the results of the present study demonstrating the effectiveness of probiotics in the treatment of CRD and those of previous studies confirming the safety of probiotics in patients undergoing chemotherapy, we recommend the use of probiotics to treat CRD.

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### Conflict of Interest

None declared.

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