

## Effects of Probiotics with or without Honey on Radiation-induced Diarrhea

H.S. Mansouri-Tehrani<sup>1</sup>, M. Rabbani Khorasgani<sup>2</sup>, M. Roayaei<sup>3\*</sup>

<sup>1</sup>Department of Biotechnology, University of Isfahan, Isfahan, Iran

<sup>2</sup>Department of Biology, University of Isfahan, Isfahan, Iran

<sup>3</sup>Department of Radiation Oncology, Isfahan University of Medical Sciences, Isfahan, Iran

### ABSTRACT

**Background:** Diarrhea is a well-recognized side effect associated with pelvic radiation; however, there is not any effective common treatment for radiation-induced diarrhea. A popular alternative is probiotics, which have been used in several gastrointestinal disorders. Probiotics are live microbial food supplements. Furthermore, honey is a putative nutritional with a variety of health effects, including antibacterial, antioxidant, anti-inflammatory and prebiotic. The present study evaluated the effects of probiotic with or without honey on radiation-induced diarrhea. **Materials and Methods:** Sixty-seven adult patients with pelvic cancer underwent radiotherapy for four weeks. They randomized to receive probiotic (n = 22), probiotic plus honey (n = 21) or placebo (n = 24) from one week before radiotherapy for five weeks. Diarrhea grade and stool consistency score were recorded weekly according to the Common Toxicity Criteria system and the Bristol scales, respectively. **Results:** The results showed a decrease in the daily number of bowel movements (p = 0.003 and 0.006), diarrhea grade (p = 0.001 and 0.001) and the need for antidiarrheal medication (p = 0.021 and 0.041) also an increase in the stool consistency (p = 0.004 and 0.005) in patients who either used probiotic or probiotic plus honey (respectively), these were significant in weeks 4 and 5 of treatment. **Conclusion:** Probiotics with or without honey can reduce the incidence of radiation-induced diarrhea and the need for antidiarrheal medication.

**Keywords:** Probiotics, honey, diarrhea, radiotherapy, pelvic cancer.

### ► Original article

**\*Corresponding author:**

Dr. Mahnaz Roayaei,

Fax: +98 31 32337964

E-mail: Roayaei@med.mui.ac.ir

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### INTRODUCTION

Pelvic radiotherapy, either alone or with chemotherapy, has established to be successful in the treatment of many of pelvic cancers. Pelvic radiation causes acute intestinal symptoms in over 80% of patients include diarrhea, nausea, and vomiting and reduces quality of life in about 50% of patients (1-3). The main adverse event of pelvic radiation is diarrhea (4-7). Cancer patients suffering from diarrhea complain of feeling fear, shame, and distress (5,8).

There is a large intestinal mucosal in the pelvic radiation field. Symptoms usually begin

during the second week of treatment (3,6,9,10) and can cause other problems such as malnutrition, abdominal pain, fecal incontinence, proctorrhagia, dehydration, weakness, stress (3,11-14) and the function of the immune system is reduced (15).

There are no prophylactic agents confirmed for the prevention of pelvic radiation enteritis (14,16). Some of nutritional regimes have been tried, but evidences are weak and limited (17,18). Radiation induced diarrhea is treated with medication such as Loperamide (19,20). Treatment failure occurs in many patients (20,21). The new methods that aim at other mechanisms in the pathophysiology of radiation-induced diarrhea

are required. Recently, probiotics are well known to have beneficial effects on intestinal problems (22-25). Studies in animal models and clinical trials of patients with inflammatory bowel disease (IBD) have frequently shown that use of probiotic organisms can effectively modulate the severity of intestinal inflammation through altering the composition and the metabolic and functional properties of gut flora (26, 27). Some clinical studies have investigated the use of probiotics for the prevention and treatment of radiation induced diarrhea (19, 21, 28-32). Probiotic literally means "for life". Probiotics are live microorganisms when ingested in sufficient numbers, they are expected to confer one or more proven health benefits on the consumer. Probiotics are supplements including viable nonpathogenic microorganisms such as *Lactobacillus* and *Bifidobacterium* to modulate the host's microflora by colonization and maintenance of the balance between pro-inflammatory and anti-inflammatory cytokines (10, 33-35). Probiotics function has actually remained unclear, although several hypotheses are being proposed. Probiotics may facilitate the production of antibacterial substances (cytokines and butyric acid), reduce the pathogenic species by creating competitive inhibition, decrease epithelial permeability to intraluminal pathogens, stimulate immune cells and create a barrier to pathogens by lowering intestinal pH. They also stimulate lactase production, which helps lactose digestion, and enhance intestinal micro flora (22-24, 36-38).

Abdominal bloating may occur in some probiotic users and occurrence of bloating may be resulted from gas production in the gastrointestinal (39).

'Prebiotics' are food ingredients that stimulate the growth and/or activity of probiotics (40). Honey properties are anti-inflammatory, antioxidant, antitumor (41-43) and effective 'prebiotic' (44-46). On the other hand, according to an old belief, patients with diarrhea to improve their problem eat yogurt (47). Also yogurt is known as a popular food carrier of probiotics (48).

There are few experiences in effect of probiotic organisms for the prevention and

treatment of radiation-induced diarrhea in cancer patients and probiotic plus honey has not been used for this purpose yet. The primary objective of this study was to evaluate the efficacy of the probiotic with or without honey in comparison with placebo, to prevent or delay the incidence of radiation-induced diarrhea. Secondary objectives were to assess if intake of probiotic with or without honey decreases the need of antidiarrheal medication as well as increases in stool consistency. Overall the main aim of research was to find more effective and with less side effect regimen for control of radiation-induced diarrhea.

## MATERIALS AND METHODS

A randomized, Placebo-Controlled Study was performed on 67 patients diagnosed with pelvic cancers (colorectal, prostate, endometr, bladder, ovary, cervix, bone sarcoma) that were referred to Radiation Oncology Clinic at Sayyed-Al-Shohada Hospital, Isfahan, Iran from October 2012 to May 2013. The treatment protocol was explained to patients and they were given informed consent to participate. Exclusion criteria included opioid usage, antimicrobial treatment and the presence of any acute or chronic gastrointestinal condition associated with diarrhea for at least one month before recruitment. Study protocol, the informed consent and materials were reviewed and approved by the Ethical Committee of the Isfahan University of Medical Sciences. This study was registered in the Iranian Registry of Clinical Trials (IRCT2015030421338N1).

All the patients were irradiated with conventional radiotherapy to a total dose from 4000 to 5000 cGy (1.8 Gy/day) with 18 MV. The upper edge of the AP field varied from the third lumbar vertebra to the first sacral bone and extended to the lower edge of the pubic bones and laterally, covering a 1.5 - 2 cm of the pelvic inlet rim, varied according to the abdominopelvic disease. Patients received conventional radiotherapy five fractions weekly for 4 -5 weeks.

Probiotic capsules 'LactoCare0' (Zist Takhmir Company, Tehran, Iran) contained: *Lactobacillus casei*  $1.5 \times 10^9$  CFU, *Lactobacillus acidophilus*  $1.5 \times 10^{10}$  CFU, *Lactobacillus rhamnosus*  $3.5 \times 10^9$  CFU, *Lactobacillus bulgaricus*  $2.5 \times 10^8$  CFU, *Bifidobacterium breve*  $1 \times 10^{10}$  CFU, *Bifidobacterium longum*  $5 \times 10^8$  CFU and *Streptococcus thermophilus*  $1.5 \times 10^8$  CFU per 500 mg. Coriander honey was obtained from Zagros Mountains (Khansar) in Iran (Keshtzare Sabz Company, Khansar, Iran). Fresh honey bee used in this study was assessed and approved by the Food and Drug Administration Isfahan University of Medical Sciences, according to Iranian National Standard No.92. Placebo capsules containing 500 mg of corn starch, with the same size, shape and color of probiotic capsules were purchased from Zist Takhmir Company, Tehran, Iran. Yogurt In packages of 150 g was purchased from Allas Dairy Company, Isfahan, Iran.

Simple randomization was used to allocate patients to three groups: group one received probiotics (two probiotic capsules per day, one capsule in the morning after breakfast and another one in the evening, after consuming 150 grams of low-fat yogurt); group two took a combination of probiotic and honey (two probiotic capsules and 30 grams honey per day, one capsule and 15 grams honey in the morning after breakfast and another one capsule in the evening, after consuming 150 grams of low-fat yogurt and 15 grams honey at night); group three was the control group received two placebo capsules per day, one capsule in the morning after breakfast and another one in the evening, after consuming 150 grams of low-fat yogurt). After randomization, the patients underwent our treatment one week before starting pelvic radiotherapy and then they continued to take the same their regime during the treatment course (in total 5 weeks).

Equal dietary recommendations, including a list of prohibited and allowed foods, were given to all the participants. All patients received the same kind and rate of low-fat yogurt and consumption of other dairy products except yogurt were not allowed. Taking antidiarrheal medication (except prescribed by the physician)

and antimicrobial drug were also prohibited; however, if patients needed to take antidiarrheal medication its consumption was recorded as an efficacy criterion.

Severity of the diarrhea was evaluated according to the Common Toxicity Criteria of the National Cancer Institute <sup>(49)</sup>: grade 1 = increase of 2-3 stools per day compared to pre-treatment, grade 2 = increase of 4-6 stools per day or nocturnal stools, grade 3 = increase of 7-9 stools per day or incontinence, grade 4 = increase of 10 or more stools, IV hydration needed. To evaluate the consistency of stool, adapted Bristol scale <sup>(50)</sup> was used to facilitate its use by patients: normal stools (Bristol 1-4), soft stools, in pieces (Bristol 5-6) and liquid stools, no shape (Bristol 7). The patients evaluated for the daily number of bowel movement (defecation), diarrhea grade, stool consistency score, the need for antidiarrheal medication and bloating weekly by one person.

Data were analyzed using: Chi-square, Fisher's exact and one-way ANOVA test. Post analysis was done by LSD (Least Significant Difference) method in order to do paired comparison (treatment group VS. placebo group). The p-value less than 0.05 was considered as statistically significant. Statistical analyses were performed using SPSS statistical software (v. 16, SPSS Inc., Chicago, IL, USA).

## RESULTS

Among 78 patients involved in this study, 11 patients were excluded for failure to follow up. Patients were aged between 20 to 85 years (mean age =  $62 \pm 14.8$  years). Patient characteristics are detailed in table 1.

### Daily number of bowel movements

The minimum and maximum daily number of bowel movements was 0 and 7 for the probiotic group, and 0 and 10 for the probiotic plus honey and placebo groups respectively. The daily number of bowel movements was higher in week 4 for the probiotic (2.8) and placebo (4.9) groups and weeks 2 and 5 for the probiotic plus honey group (2.5). The results of the linear

mixed model test showed that the mean daily number of bowel movements in the placebo group was significantly higher than the probiotic and probiotic plus honey groups throughout the treatment course ( $p = 0.003$  and  $p = 0.006$  respectively) (figure 1).

### Diarrhea grade

Moderate to severe diarrheal symptoms (grades 2, 3) was recorded in 31 (46.3%) patients during pelvic radiotherapy. The number (percentage) patients with diarrhea grades 2 and 3 was 7 (31.8), 4 (19) and 17 (70.8) during the treatment for the probiotic, probiotic plus honey

and placebo groups respectively. The results of Mann-Whitney test showed that the mean diarrhea grade in weeks 4 and 5 was significantly higher in the placebo group than the probiotic and probiotic plus honey groups ( $p = 0.007$  and  $0.001$  for probiotic and  $p < 0.001$  and  $p = 0.001$  for probiotic plus honey in weeks 4 and 5 respectively) as shown in figure 2. Fisher's exact test also revealed that patients in the placebo group were diagnosed with grade 2 diarrhea, significantly, earlier than the probiotic ( $P = 0.016$ ) and probiotic plus honey groups ( $P = 0.005$ ).

Table 1. Patient characteristics.

	Study arms			P
	Probiotic	Probiotic- Honey	Placebo	
	(n=22 )	(n=21 )	(n=24 )	
Age (mean $\pm$ SD)	63.73 $\pm$ 15.09	57.86 $\pm$ 17.48	64.17 $\pm$ 11.69	.44 <sup>a</sup>
Gender				.15 <sup>b</sup>
male	14 (20.9)	8 (11.9)	17 (25.4)	
female	8 (11.9)	13 (19.4)	7 (10.4)	
Cancer type				.42 <sup>c</sup>
colorectal	6 (9.0)	9 (13.4)	9 (13.4)	
prostate	6 (9.0)	3 (4.5)	6 (9.0)	
endometrial	3 (4.5)	5 (7.5)	2 (3.0)	
bladder	4 (6.0)	0	4 (6.0)	
ovary	2 (3.0)	1 (1.5)	1 (1.5)	
cervical	1 (1.5)	1 (1.5)	2 (3.0)	
bone sarcoma	0	2 (3.0)	0	
ChRt (yes)	8 (11.9)	9 (13.4)	9 (13.4)	.9 <sup>b</sup>

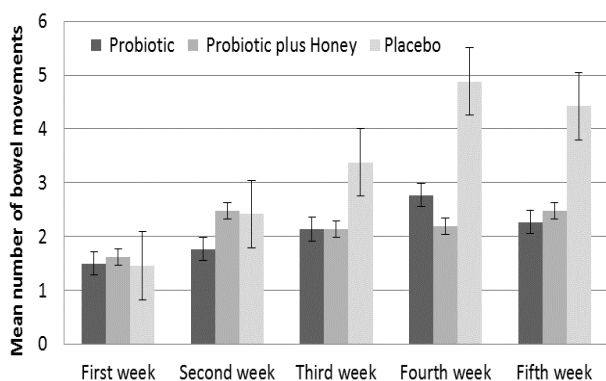


Figure 1. Comparison of the mean number of bowel movements per week during pelvic radiotherapy. Standard error bars were used. Linear mixed model test ( $p = 0.003$  and  $p = 0.006$  for the probiotic and probiotic plus honey groups respectively).

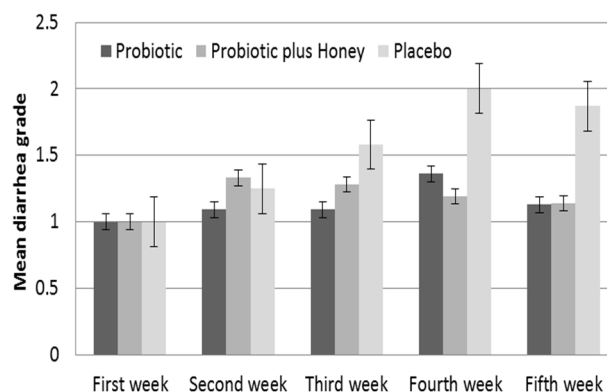


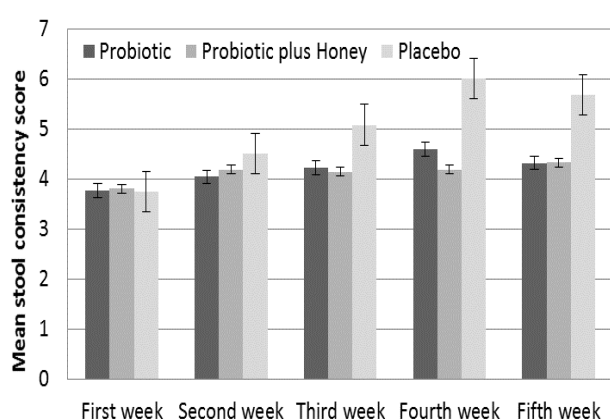
Figure 2. Comparison of the mean diarrhea grade per week during pelvic radiotherapy. Standard error bars were used. Mann-Whitney test ( $p = 0.007$  and  $0.001$  for probiotic and  $p < 0.001$  and  $p = 0.001$  for probiotic plus honey in weeks 4 and 5 respectively).

### Stool consistency

The mean stool consistency was initially 3.8 for all groups. During the treatment, mean consistency stool was 4.3 for the probiotic and probiotic plus honey groups and 5.7 for the placebo group. The results of Mann-Whitney test showed that the mean stool consistency score in the probiotic and the probiotic plus honey groups were significantly lower than the placebo group in weeks 4 and 5 of treatment ( $p=0.003$  and  $0.004$  for the probiotic group and  $p<0.001$  and  $p=0.005$  for the probiotic plus honey group in weeks 4 and 5 respectively) (figure 3).

### The need for antidiarrheal medication

During pelvic radiotherapy was found that antidiarrheal medication is required for 13 (19.4%) patients. Among all patients, 9.1%, 9.5% and 37.5% belonged to the probiotic, probiotic plus honey and placebo groups respectively needed for antidiarrheal medication. In the first week no patients needed for antidiarrheal medication. Only one and two patients in the fifth week needed for antidiarrheal medication in the probiotic and probiotic plus honey respectively. The number of patients who needed for antidiarrheal medication in the placebo group was one, four, three, one in weeks 2, 3, 4, 5 respectively. The Fisher's exact test showed that the number of patients who needed to antidiarrheal medication

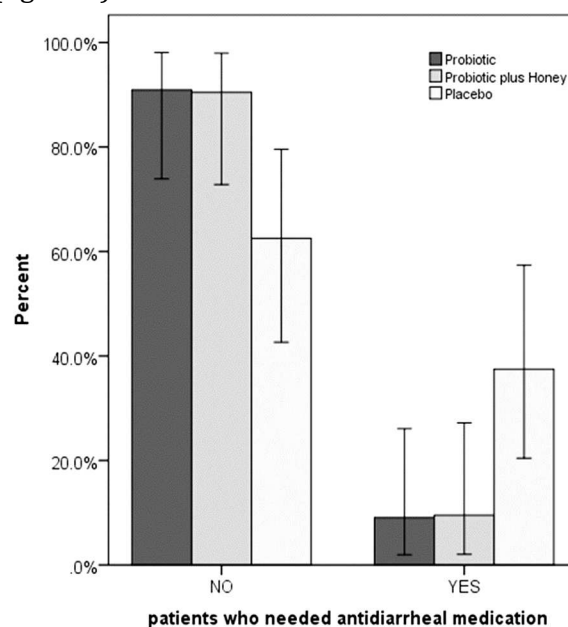


**Figure 3.** Comparison of the mean stool consistency score per week during pelvic radiotherapy. Standard error bars were used. Mann-Whitney test ( $p=0.003$  and  $0.004$  for the probiotic group and  $p<0.001$  and  $p=0.005$  for the probiotic plus honey group in weeks 4 and 5 respectively).

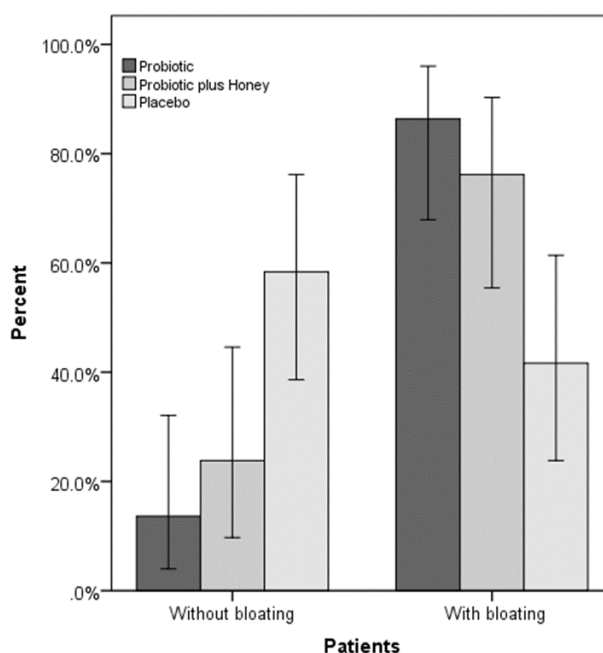
in the placebo group was significantly higher than the probiotic ( $P=0.038$ ) and probiotic plus honey groups ( $P=0.04$ ) (figure 4). The result of Fisher's exact test also indicated that patients in the groups that received probiotic used antidiarrheal medication later than the placebo group ( $P=0.021$  and  $P=0.041$  for the probiotic and probiotic plus honey respectively).

### Adverse effects

Some of probiotics users reported stomach pain and bloating. During pelvic radiotherapy, three patients (they belonged to probiotic user; with or without honey) complained of upper abdominal pain. The causal link between the complaint and the probiotic was not investigated. During the treatment 45 patients complained of bloating (19 patients of the probiotic group, 16 patients of the probiotic plus honey group and 10 patients in the placebo group). The results of the Chi-square test showed that the number of patients with bloating in the probiotic groups (alone or plus honey) was significantly higher than the placebo group ( $P=0.002$  and  $0.021$  for the probiotic and the probiotic plus honey groups, respectively) (figure 5).



**Figure 4.** Comparison of patients who needed antidiarrheal medication and those who did not during pelvic radiotherapy. Fisher's exact test ( $P=0.038$  and  $P=0.04$  for the probiotic and probiotic plus honey groups, respectively).



**Figure 5.** Comparison of patients with and without bloating during pelvic radiotherapy. Chi-square test ( $P=0.002$  and  $0.021$  for the probiotic and the probiotic plus honey groups, respectively).

## DISCUSSION

Diarrhea is most (80%) and worst side effect of pelvic radiotherapy<sup>(1-3)</sup>. Different studies have focused on the prevention or control of radiation-induced diarrhea. In the current study probiotic with or without honey were used in patients undergoing pelvic radiotherapy.

Some studies show significant beneficial effects of probiotics on control of radiation-induced diarrhea; Delia *et al.*<sup>(19,51)</sup> and Timko<sup>(31)</sup>. The benefits of probiotic therapy with VSL#3 (probiotics, including: *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbruekii subsp. Bulgaricus*, *B. longum*, *B. breve*, and *B. infantis*, *Streptococcus salivarius subsp. Thermophiles*) have been recorded in 490 patients during radiotherapy after surgery for the abdominal and pelvic cancer in a double-blind, placebo- controlled trial. The mean daily number of bowel movements in these 490 patients was  $4.6 \pm 2$  and  $12.3 \pm 4$  in VSL#3 and placebo recipients, respectively<sup>(19)</sup>. Similarly, a randomized study has demonstrated a decrease in the mean number of bowel movements ( $p<0.05$ ) and a decrease in the incidence of diarrhea ( $p<0.01$ ) in patients undergoing pelvic radiotherapy and

taking *Lactobacillus acidophilus*<sup>(29)</sup>. Another randomized placebo controlled nutrition trial reported that yogurt containing *Lactobacillus casei* DN-114 001 significantly improved the consistency of stool, without reducing the incidence of radiation-induced diarrhea<sup>(21)</sup>.

The mean of bowel movement frequency in our study was 2.09 and 2.18 per day in the probiotic and probiotic plus honey groups respectively and 3.32 in the placebo group, which is obviously lower to the 5.1 and 14.7 per day in the VSL#3 and placebo groups respectively reported by Delia *et al.*<sup>(19,51)</sup>, but results of Timko *et al.* study (4.16 in the probiotic group and 2.52 in the Hylak Tropfen Forte group)<sup>(31)</sup> were closer to our study. Some investigators considered stool consistency, rather than frequency of bowel movement, to be a more appropriate measure of diarrhea<sup>(52)</sup>. In this study, the stool consistency was normal (score 4.3 in Bristol scale) for the probiotic and probiotic plus honey groups and soft (score 5.7 in Bristol scale) for the placebo group, which is obviously lower than stool consistency score in the probiotic (taking liquid yogurt containing *L. casei* DN-114 001 at  $10^8$  CFU/g) and placebo groups in Giralt *et al.* study<sup>(21)</sup>. In Giralt *et al.*

study over 80% of patients undergoing pelvic radiotherapy reached the worse stool consistency score (6 and 7 in Bristol scale), without significant difference between the two (probiotic and placebo) groups<sup>(21)</sup>. Since some studies show that yogurt is effective in the treatment of diarrhea<sup>(47)</sup> and it is as probiotic carrier food<sup>(48)</sup>, low-fat yogurt taking in our study may be a reason for the difference of the number of bowel movements and stool consistency score between this study and similar studies<sup>(19,53)</sup> in the patients who underwent pelvic radiotherapy. More controlled clinical trials are needed to confirm this issue.

In the present study patients who need for antidiarrheal medication in the probiotic and probiotic plus honey groups were significantly less than the placebo group, also in Timko *et al.* study 27% in the probiotic group and 55% in the Hylak Tropfen Forte group needed for antidiarrheal medication<sup>(31)</sup>. The first prescription of antidiarrheal medication in the Delia *et al.* study<sup>(19)</sup> was in the VSL#3 group significantly later than in the control group, which this result was similar to our study. Although we expected probiotic plus honey is more effective than probiotic alone, but statistically significant difference was not found. This finding may have resulted from effect of honey as prebiotic needed prolonged time to improve probiotics. No similar study has been found.

Important differences between our study and other studies are the treatment protocols, onset of intake as well as dosages, species and strains of probiotics. The most commonly used strains of probiotics in reported researchs are *Lactobacillus*, *Bifidobacterium* and *Cocci*<sup>(22,23,25,36)</sup>. Since bloating may be a side effect of probiotics use<sup>(39)</sup>, in this study bloating was asked the patients. These results showed that patients taking probiotics suffered from bloating more than the control group during the treatment. However, the severity of the symptom was not enough to discontinue the use of probiotics. In the similar studies that have investigated effects of probiotics on diarrhea, bloating has not evaluated.

Our result showed that probiotics improved

the quality of life of patients undergoing pelvic radiation. So probiotic usage can prevent premature discontinuation of pelvic radiation and increase radiation dose if need be. The verification of beneficial use of probiotics in patients undergoing radiation needs more clinical trial. Since probiotics (with or without honey) did not completely prevent moderate to severe diarrhea during treatment, this study suggest that probiotics are used as a beneficial supplement to reduce pelvic radiation-induced diarrhea.

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**Conflict of interest:** Declared None

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