



Sage tea–thyme–peppermint hydrosol oral rinse reduces chemotherapy-induced oral mucositis: A randomized controlled pilot study



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ABSTRACT

Objective: This pilot study aimed to investigate the preventive effect of sage tea–thyme–peppermint hydrosol oral rinse used in conjunction with basic oral care on chemotherapy-induced oral mucositis.

Design: An open-label randomized controlled study.

Setting: Two oncology hospitals in Ankara, Turkey.

Interventions: Patients receiving 5-fluorouracil-based chemotherapy regimens were divided into the intervention group (N = 30) and control group (N = 30). Basic oral care was prescribed to the control group, while the intervention group was prescribed sage tea–thyme–peppermint hydrosol in addition to basic oral care. All patients were called to assess their compliance with the study instructions on day 5 and 14. **Main outcome measures:** Oral mucositis was evaluated using an inspection method or by assessing oral cavity photos based on the World Health Organization oral toxicity scale on day 5 and 14.

Results: Most of the patients in the intervention group did not develop oral mucositis on day 5. In addition, the incidence of grade 1 oral mucositis was statistically lower in the intervention group (10%) than the control group (53.3%) on day 5. By day 14, the majority of patients in both the groups had grade 0 oral mucositis.

Conclusions: Sage tea–thyme–peppermint hydrosol oral rinse has promising results in alleviating oral mucositis. This hydrosol can be recommended for clinical use as it is well tolerated and cost-effective. However, further randomized controlled trials are needed to support the study.

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1. Introduction

Oral mucositis, an inflammatory and potentially ulcerative process, adversely affects the mucous membrane of the oral cavity in patients undergoing chemotherapy. Specifically, chemotherapy drugs facilitate the infiltration of microorganisms that disrupt the function of serous mucous glands.¹ Oral mucositis may cause erythema, edema, and atrophy of the oral mucosal epithelium.² Although the incidence of oral mucositis is reported to be 5%–15% overall among patients, the observed incidence varies depending on the treatment and risk factors.^{3,4} The incidence of oral mucositis can increase significantly with the use of high-risk drugs such as 5-fluorouracil (5-FU). Approximately 40%–60% patients receiving 5-

FU develop oral mucositis. Along with high incidence, the grades of 5-FU induced oral mucositis can reach 3–4 with a ratio of 10–15%.^{5,6}

Oral mucositis is one of the most debilitating and troublesome toxicities, causing mouth discomfort, pain, nutritional deficits, weight loss, and the delay of treatment, leading to a low quality of life in patients undergoing chemotherapy.^{2,7,8} In addition, oral mucositis poses a serious risk for the development of life-threatening infections such as bacteremia and septicemia.^{9,10} Therefore, to prevent any occurrence of this condition, clinically effective prophylactic procedures should be developed and employed. Within this scope, there are several different approaches to mouth care which might prevent oral mucositis. Despite the lack of supporting evidence, basic oral care has been recommended in clinical guidelines.¹¹ In addition to basic oral care, a variety of treatments have been reported to prevent oral mucositis.^{8,12–18} These preventive treatments include the use of solutions such as chlorhexidine, chamomile, black mulberry syrup, and honey; treatment modalities such as cryotherapy and low-energy helium–neon

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laser therapy; and supplements such as selenium, zinc sulfate, vitamins A and E, cytokine-like agents, and growth factors. However, despite the implementation of strict mouth care procedures, patients undergoing chemotherapy regimens frequently suffer from increased incidence of oral mucositis.^{6,19,20} Therefore, it is necessary to develop additional methods that complement basic oral care for the prevention of oral mucositis.

In traditional medicine, patients with cancer used sage tea, thyme and peppermint for the prevention of oral mucositis.^{14,21,22} These herbs have antiseptic,^{23–25} anti-inflammatory,^{23–25} antimicrobial,^{23,24,26,27} antifungal,^{23,27,28} and antiviral,^{24,28} properties. In addition, these herbs are effective as a mouth-wash or mouth rinse against stomatitis,^{24,25} pharyngolaryngitis, and oral candidiasis.²⁹ However, to the best of our knowledge, no study has thus far evaluated the effects of these herbs on chemotherapy-induced oral mucositis. Therefore, considering the paucity of research on effective prophylactic approaches for the avoidance of oral mucositis and on the effects of sage tea, thyme, and peppermint on improving oral mucosal health, further studies investigating the prophylactic effect of these herbs on oral mucositis are warranted.

Extracts, essential oils or hydrosols of these plants can be used for medicinal purposes. Hydrosols, known as floral water, distillate water or herbal aromatic water, are the by-products of hydro and steam distillation of different parts of plant materials. In general, hydrosols comprise the water-soluble components of the extracted essential oil^{30,31} and they demonstrate a longer shelf-life compared to other extracts.^{32,33} Hence, the present study was designed to examine the effect of sage tea–thyme–peppermint hydrosol oral rinse combined with basic oral care on the prevention of chemotherapy-induced oral mucositis.

2. Materials and methods

2.1. Subjects and study design

The research was conducted in the outpatient chemotherapy units of two oncology hospitals in Ankara, Turkey. The study population comprised patients receiving 5-FU-based chemotherapy regimens (bolus or infusion). The inclusion criteria were as follows: 18–65 years of age, receiving either bolus or infusion 5-FU-based chemotherapy regimens, platelet counts over 20,000/ μL , no oral mucositis upon inspection (according to the World Health Organization [WHO] oral toxicity scale), permission provided for photos to be taken of their oral cavity, and voluntary participation in the study. The criteria for exclusion included receiving head and neck radiotherapy and exhibiting an allergy to sage tea, thyme, or peppermint.

Of the 78 assessed individuals, 13 were excluded because of their ineligibility (>65 years of age) and 5 refused to participate because of their dislike of the hydrosol odor. Therefore, 60 patients were randomly allocated into the study groups. To accomplish this, the first patient was assigned to the control group and the next one to the intervention group and so on. The statistical power for our sample size was 0.95 and the margin of error was 0.05. The design was an open-label randomized controlled trial. A placebo was not used since the sage tea–thyme–peppermint hydrosol has a characteristic odor and taste.

2.2. Measurement tools

Data were collected using a patient questionnaire, the WHO oral toxicity scale, oral cavity photos of the patients, and intervention and control group compliance checklists. The patient questionnaire, which was developed from a questionnaire used

extensively in previous studies,^{6,7,19,34,35} contained questions on socio-demographic characteristics (age, gender, and educational level), patient-related risk factors (current smoking habits, daily liquid consumption, and dental prosthesis), and treatment-related risk factors (diagnosis, chemotherapy regimen, and dose). To grade oral mucositis, the WHO oral toxicity scale was utilized.³⁶ This tool categorizes grades of oral mucositis as follows: grade 0 (no mucositis); grade 1 (soreness and erythema, no further symptoms); grade 2 (ulcers present, but solid diet possible); grade 3 (ulcers present, required a liquid diet) and grade 4 (severe mucositis preventing oral nutrition and necessitating total parenteral nutrition).³⁶ Although the WHO oral toxicity scale has been widely used in many studies and clinical practices,^{6,17,37,38,39} it has never been subjected to rigorous validation tests. Use of this empirical scale has been verified by 40 years of accumulated experiences (and the rationale for its use coincides with the opinions of most experts). However, several additional oral mucositis assessment scales have been derived based on the WHO oral toxicity scale.^{40,41,42}

The inspection of oral mucosa and oral cavity photos was independently performed by two researchers. If the patients attended the hospital on days 5 and 14, oral mucositis was assessed using the manual inspection method, but if the patients did not attend hospital on the aforementioned monitoring days, oral mucositis was evaluated using photos taken by the patients' relatives. The presence of visible ulcers was the key feature to distinguish between grade 1 and grade 2 mucositis. The intervention and control compliance checklists included blank spaces to be completed during the 14-day study period. The control group compliance checklist comprised basic oral care instructions, while the intervention group compliance checklist, contained directions for the use of sage tea–thyme–peppermint hydrosol oral rinse in addition to basic oral care instructions.

2.3. Preparation of the sage tea–thyme–peppermint hydrosol

Sage tea, thyme and peppermint hydrosols were obtained from an essential oil producing company. After mixing equal amounts of these hydrosols, the mixture was analyzed at the Pharmacognosy Department, Ankara University Faculty of Pharmacy. Gas chromatography (GC) analysis using the Agilent 6890N Network GC system was used to check the quality of the hydrosol. According to the GC analysis, the major constituents of the hydrosol included 2-hexanone, eucalyptol, menthone, camphor, pulegone, menthol, α -terpineol, piperitenone, thymol and carvacrol. Following analysis, the mixed hydrosol was transferred to light-proof glass bottles using an aseptic technique. These bottles were then stored in cool, dark conditions. Instructions were provided to patients indicating that once the bottles were opened, the bottles were to be kept in a refrigerator.

2.4. Data collection and intervention

On the first day of chemotherapy, the patient questionnaires of both groups were filled out by the researchers; this process took approximately 10 min. Subsequently, patients in the control group were informed about basic oral care using a leaflet. Using another leaflet, the intervention patients were provided with information about basic oral care and with information about using sage tea–thyme–peppermint hydrosol oral rinse. Both leaflets were developed by the researchers based on literature.^{14,16,23}

The leaflet for control patients included the following basic oral care instructions: rinse the mouth out with saline four times a day for 30 s and brush the teeth twice a day for 14 days starting on the first day of chemotherapy. The leaflet for intervention patients included the aforementioned basic oral care instructions and also

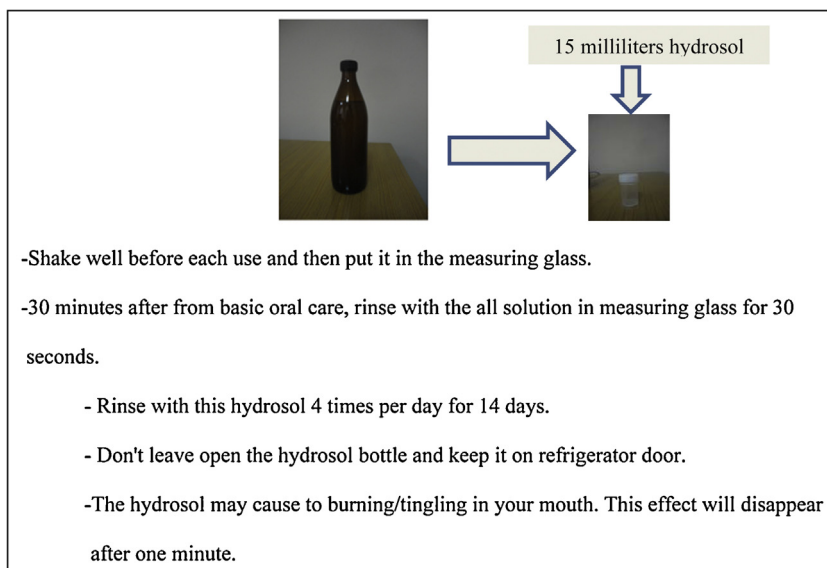


Fig. 1. Instruction guide for the using sage tea-thyme-peppermint hydrosol.

The first photo stands for 500 mL light-proof glass bottle filled with sage tea-thyme-peppermint hydrosol and the second one stands for the measurement glass. Arrows indicate that patients should put the 15 mL hydrosol in the measurement glass.

instructions for an oral rinse of the mouth four times a day for 30 s using 15 mL of sage tea-thyme-peppermint hydrosol (Fig. 1). The hydrosol oral rinse was administered 30 min after the basic oral care procedure was completed. Again all procedures continued for 14 days starting on the first day of chemotherapy.

On the first day of treatment, an ultra-soft tooth brush and a tooth paste containing fluoride were given to all patients to ensure standardization. Two light-proof glass bottles, each containing 500 mL sage tea-thyme-peppermint hydrosol oral rinse, and a 15 mL measuring glass were given to the patients in the intervention group. Since chemotherapy-induced oral mucositis generally develops within 4–7 days of initiation of the chemotherapy regimen and exacerbates within 2 weeks,³⁵ the oral cavity of all patients was examined on days 5 and 14 using the manual inspection method (or, where necessary, by assessing photos taken by the patients' relatives). On the first day of chemotherapy, patients' relatives were instructed about how to take pictures of the relevant areas. This was accomplished through a leaflet containing eight photo samples, i.e., anterior/posterior region of the tongue, right/left buccal mucosa, upper/lower labial mucosa, floor of mouth, and palate. The relatives were asked to send the photos via e-mail or the WhatsApp Messenger® program to the researchers. In total, three patients in the intervention group and six patients in the control group were assessed by photos provided on day 5 and 14. All other patients were examined by the manual inspection method.

Oral care compliance was assessed through self-reporting by patients. All of the patients in the intervention group were telephoned by the researchers during the 14 days (starting on the first day of chemotherapy) to assess compliance with the study instructions. During each phone call, patients were asked about the frequency and duration of rinsing with saline and hydrosol and the frequency of brushing their teeth. All of these parameters were marked daily on the intervention group compliance checklist during the study period. Likewise, similar telephone call procedures were followed for the control group. (Fig. 2). The compliance rate was calculated according to data on the checklists. Control (96.7%) and intervention (93.3%) groups achieved high compliance during the study.

2.5. Data analysis

All data were analyzed using SPSS (Statistical Program for Social Sciences) version 17.0. Percentages, frequencies, mean, and standard deviation were used to define sample characteristics. The characteristics of the control and intervention groups were compared using Student's *t*-test and the Mann-Whitney *U* test. Chi-square and Fisher's exact tests were used for categorical data analysis. Cohen's kappa coefficient was used to analyze inter-rater reliability. Kappa values ≤ 0 were considered as "no agreement," 0.01–0.20 as "none to slight," 0.21–0.40 as "fair," 0.41–0.60 as "moderate," 0.61–0.80 as "substantial," and > 0.80 as "almost perfect agreement."⁴³ The statistical significance levels were considered at $p < 0.05$ and 0.001 for analyses.

2.6. Ethical considerations

This study was approved by the Human Research Ethics Committee of Turgut Ozal University and was performed in accordance with the Helsinki Declaration and local requirements. Before commencing the study, the research aim was explained to all patients and written informed consent was obtained. The participants could withdraw from the study at any time, and they were not expected to pay for anything.

3. Results

3.1. Sample characteristics

The mean age of the patients in the intervention group was 52.6 ± 8.2 years and that in the control group was 48.7 ± 10.0 years. The majority of the patients in the intervention (63.3%) and control (56.7%) groups were female, nearly all of which in both the intervention (90.0%) and control (93.3%) groups were married. The proportions that were primarily educated was 46.7% in the intervention group and 53.6% in the control group.

Most of the patients in both groups brushed their teeth more than twice a day prior to the initiation of treatment (50.0% in the intervention group and 43.3% in the control group). Moreover, the majority did not have any dental disease (63.3% in the intervention

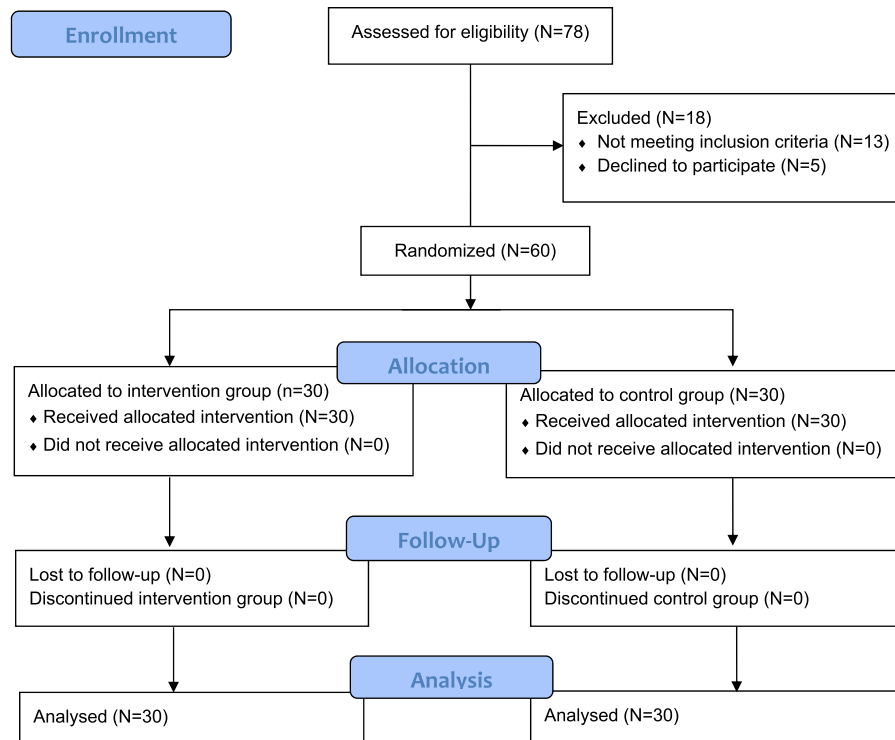


Fig. 2. Flow chart of study protocol.

Arrows indicate that steps of the study protocol consecutively.

group and 66.7% in the control group). Patients in the intervention group consumed 2.44 ± 0.7 L of liquid daily, and those in the control group consumed 2.22 ± 0.7 L. No patient had any recent history of smoking. Approximately half of the patients in both groups (60% of the intervention group and 40% of the control group) have dentures. The most prevalent diagnosis in the intervention (60.0%) and control (46.7%) groups was colon cancer. The majority of the patients in both groups received FOLFIRI (30.0% in the intervention group and 30.0% in the control group) and FOLFOX (30.0% in the intervention group and 26.7% in the control group) as chemotherapy regimens (Table 1).

There was no statistically significant difference between the groups in terms of age, gender, educational status, tooth brushing habits, dental disease, denture wearing, or smoking habits ($p > 0.05$). Regarding the chemotherapy protocols both groups were found to be similar in terms of 5-FU dosage ($p > 0.05$).

3.2. Development of oral mucositis in the intervention and control groups

According to kappa analysis, the evaluations performed by both the researchers on days 5 and 14 were in accordance with each other (kappa coefficient: 0.98 and 0.85, respectively). Oral mucositis was not observed in 70% patients in the intervention group compared with 40% patients in the control group on day 5 (Fig. 3). Accordingly, the development of oral mucositis decreased in the intervention group compared to the control group. In addition, grade 0 oral mucositis was observed in almost all patients on day 14 (93.3% in the intervention group and 96.7% in the control group), and there was no statistically significant difference between the groups ($p > 0.05$) (Fig. 4).

During the study, only grades 1 and 2 oral mucositis was observed among patients in both the groups. The incidence of grade 1 oral mucositis was statistically lower in the intervention group (10%) than the control group (53.3%) on day 5 ($p < 0.001$). The incidence of grade 2 oral mucositis was slightly higher in the

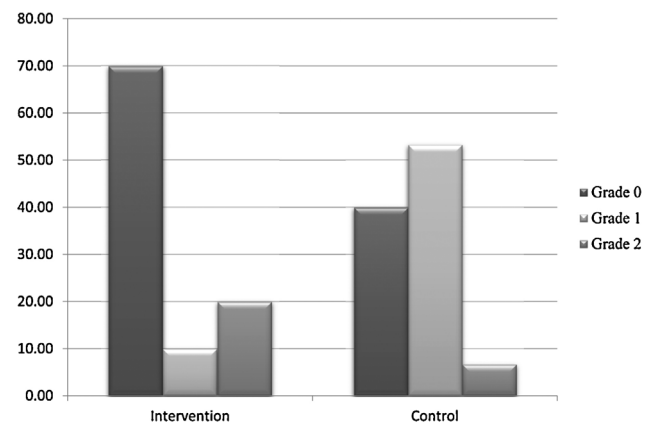


Fig. 3. Grades of oral mucositis on 5th day. N = 30 for intervention and control group. Grades of oral mucositis (%).

intervention group (20.0%) than the control group (6.7%) on day 5 (Table 2). Although not shown in the table, statistical analysis showed that the difference of grade 2 oral mucositis was not statistically significant ($X^2: 0.494$ $p: 0.689$).

4. Discussion

In this study, the effect of sage tea–thyme–peppermint hydrosol oral rinse was evaluated for the prevention of chemotherapy-induced oral mucositis. To our best knowledge, this is the first report examining the effect of this hydrosol on chemotherapy-induced oral mucositis. The main findings of the study reveal that the incidence of oral mucositis was significantly lower in the intervention group compared to the control group on day 5. Considering this finding, sage tea–thyme–peppermint hydrosol oral rinse might reduce the incidence of oral mucositis.

Table 1
Socio demographic and medical characteristics of the sample.

Socio-demographic and Determining Characteristics	Groups			
	Intervention		Control	
	N	%	N	%
Age (Mean ± SD)	52.6 ± 8.2		48.7 ± 10.0	
Daily liquid consumption(Mean ± SD)	2.44 ± 0.7		2.22 ± 0.7	
Gender				
Male	11	36.7	13	43.3
Female	19	63.3	17	56.7
Marital status				
Married		90.0	28	93.3
Single	3	10.0	2	6.7
Educational status				
Primary school	14	46.7	15	53.6
High school	8	26.7	9	25.0
University	8	26.7	6	21.4
Smoking habits				
Yes	–	–	–	–
Quitted	13	43.3	15	50.0
No	17	56.7	15	50.0
Brushing teeth				
None	7	23.3	4	13.3
One time	8	26.7	13	43.3
Two or more	15	50.0	13	43.3
Having denture				
Yes	18	60.0	12	40.0
No	12	40.0	18	60.0
Having dental disease				
Yes	11	36.7	10	33.3
No	19	63.3	20	66.7
Medical Characteristics				
Diagnose				
Colon cancer	18	60.0	14	46.7
Rectal cancer	3	10.0	6	20.0
Esophageal cancer	1	3.3	1	3.3
Gastric cancer	1	3.3	3	10.0
Breast cancer	7	23.4	6	20.0
Chemotherapy regimen				
FOLFIRI (Leucovorin + 5-FU + Irinotecan)	9	30.0	9	30.0
FOLFOX (Leucovorin + 5-FU + Oxaliplatin)	9	30.0	8	26.7
CAF (Cyclophosphamide + Doxorubicin + 5-FU)	5	16.6	5	16.6
TCF (Docetaxel + Cyclophosphamide + 5-FU)	3	10.0	3	10.0
FUFA (5-FU+ Leucovorin)	2	6.7	4	13.3
FEC (5-FU + Epiribucin + Cyclophosphamide)	2	6.7	1	3.3

Table 2
The incidence of oral mucositis in intervention and control groups on 5th and 14th days.

Grade	5th Day				14th Day			
	Intervention		Control		Intervention		Control	
	N	%	N	%	N	%	N	%
0	21	70.0	12	40.0	28	93.3	29	96.7
1	3	10.0	16	53.3	1	3.3	1	3.3
2	6	20.0	2	6.7	1	3.3	–	–
3	–	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–	–
Total	30	100.0	30	100.0	30	100.0	30	100.0
Statistical Values		X ² : 12.921				X ² : 1.229		
		p: 0.001				p: 0.742		

Since microbial colonization aggravates the severity of oral mucositis, oral decontamination can be used to reduce oral mucositis.^{8,35} Sage tea, thyme, and peppermint have antiseptic,^{23,24} anti-inflammatory,^{23–25} antimicrobial,^{23,24,26,27} antifungal^{23,27,28} and antiviral^{24,28} properties. Therefore, the lower incidence of oral mucositis on day 5 in the intervention group likely results from

the effects of hydrosol. Our finding implies that using hydrosol oral rinse along with basic oral care is more effective than using only basic oral care for maintaining good oral hygiene.

The present study revealed that the incidence of oral mucositis was 30% in patients using the sage tea–thyme–peppermint hydrosol. Thus far, no studies have specifically evaluated the

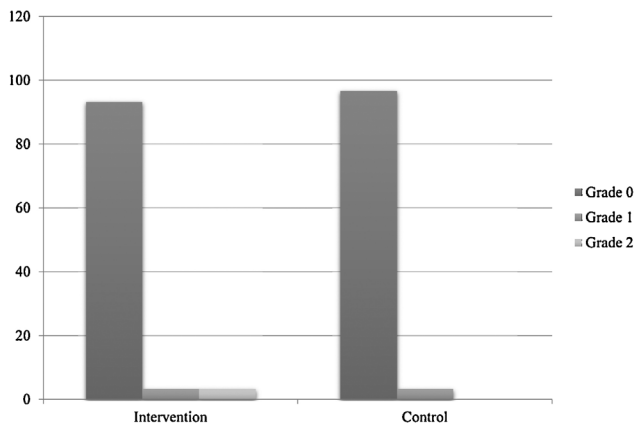


Fig. 4. Grades of oral mucositis on 14th day. N = 30 for intervention and control group. Grades of oral mucositis (%).

prophylactic impact of sage tea, thyme, and peppermint on chemotherapy-induced oral mucositis. However, studies have been conducted to evaluate the effects of other complementary attempts such as chamomile, black mulberry syrup, kefir, and Chinese herbs on chemotherapy-induced oral mucositis.^{20,22,44,45} In these studies, the incidence of oral mucositis varied between 23.3% and 40%. Considering the results presented here, the incidence of oral mucositis was comparable to that of the previous reports.

The present study revealed that the occurrence of oral mucositis was quite high on day 5 in the control group. Consistent with this finding, oral mucositis has been reported to develop in as many as 80% 5-FU recipients.⁴⁶ In addition, a recent randomized study conducted on 5-FU recipients found that the incidence of oral mucositis was high (60%) in the control group (in agreement with our study).⁶ In contrast to our results, the incidence of oral mucositis in the control groups receiving 5-FU was lower than the treatment group in some studies, i.e., 21.6%,³⁶ 36.7%,²⁰ and 43.3%.⁴⁷ This difference may be attributed to the different sample characteristics.

It is imperative that evidence-based methods for preventing chemotherapy-induced oral mucositis should be improved. There is a significant need for a prophylactic approach towards this issue. Sage tea–thyme–peppermint hydrosol oral rinse has shown promising results in reducing oral mucositis. The hydrosol used in this study is a well-tolerated, feasible, cost-effective, safe, and non-invasive method. However, some limitations to our study do need to be noted. Lack of blinding and a follow up procedure lasting only one cycle of chemotherapy were major limitations. In addition, assessing oral care compliance by self-report of patients was also a limitation for this study.

5. Conclusions

Most patients had colon cancers and received FOLFIRI and FOLFOX chemotherapy regimens. The most striking finding was that the use of sage tea–thyme–peppermint hydrosol reduced the incidence of oral mucositis. Oral mucositis did not occur in 70% patients in the intervention group and 40% patients in the control group on day 5. Therefore, sage tea–thyme–peppermint hydrosol may help in maintaining good oral hygiene and in preserving the integrity of the oral mucosa. However, further randomized controlled clinical trials are needed to validate the findings of this study.

Conflict of interest

The authors have no conflicts of interest to disclose.

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