

The Effect of Oral Care With Black Mulberry Extract on Oral Mucositis, Dry Mouth, and Weight Gain in Patients With Cancer

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BACKGROUND: For patients receiving chemotherapy, various oral care therapies are used to treat oral mucositis, but the use of black mulberry extract as an effective treatment has not been widely studied.

OBJECTIVES: This study examined whether black mulberry extract is an effective treatment for oral mucositis, dry mouth, and weight gain compared to sodium bicarbonate in patients with cancer.

METHODS: The control group (N = 20) received sodium bicarbonate, and the intervention group (N = 20) received black mulberry extract. Mucositis and weight gain were evaluated on days 1, 7, and 15 after oral care application.

FINDINGS: For both groups, mean scores indicated a statistically significant decrease in mucositis and dry mouth at all three time points. Mean scores were significantly lower in the intervention group on days 7 and 15. At all three time points, increases in weight were statistically significant for the intervention group but not for the control group. Increased weight gain in the intervention group was statistically significant when comparing the two groups on days 7 and 15.

KEYWORDS

black mulberry extract; oral mucositis; weight gain; dry mouth

DIGITAL OBJECT IDENTIFIER

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BECAUSE ORAL MUCOSA EPITHELIAL CELLS DIVIDE MORE RAPIDLY than other cells, chemotherapeutic agents suppress the growth and maturation of cells and disrupt the primary mucosal barrier in the mouth and throat (Shumsky et al., 2019). As a result, oral mucositis can develop. Oral mucositis can lead to deterioration in the mucosal barrier; weakening of the oral mucosal epithelial cells; erythema; edema; bleeding; ulcerations; hoarseness; and difficulty speaking, chewing, and swallowing (Shimamura et al., 2018). Oral mucositis typically occurs within one week after chemotherapy administration and heals after 21 days (Bahar et al., 2019). Weight loss, dehydration, ulceration of the mucosa, and fluid–electrolyte imbalance may develop in patients who are undernourished (Eduardo et al., 2018). The presence of mucositis can cause patients to experience severe pain in the oral cavity and/or throat, which impairs their ability to chew, swallow, and speak, leading to inadequate fluid–nutrient intake, malnutrition, and communication problems (Lee et al., 2020; Silva et al., 2021). These symptoms and side effects can increase the length of patient hospital stays and treatment costs, as well as cause patients' quality of life to deteriorate (Fernández-Rodríguez et al., 2019; Pereira et al., 2018).

Various pharmacologic and nonpharmacologic oral care methods and therapies are used in the treatment of oral mucositis (Lim & Choi, 2019; Thakur et al., 2020). In a study conducted in Turkey, the most common substances used to prevent mouth sores in patients with cancer receiving chemotherapy included chlorhexidine gluconate mouthwashes (68.2%); sodium bicarbonate (54.2%); saltwater (51.7%); sage, chamomile, and fennel tea (46.7%); water with lemon (27.5%); black mulberry molasses (26.7%); honey (24.2%); and turmeric (17.5%) (Berk et al., 2020). Black mulberry has anti-inflammatory, antioxidative, and analgesic effects (Li et al., 2018; Liu et al., 2021). Black mulberry contains papiriflavalon A, kuraridin, saforaflavanon D, and saforaiso flavanon A, all of which can provide antifungal and strong antimicrobial activity and are particularly effective in the healing of mouth and dental wounds (Sireesha & Sri, 2021). Doğan et al. (2017) also reported that black mulberry molasses prevents oral mucositis by 38%, delays the formation of mucositis, and reduces the severity of mucositis in patients undergoing radiation therapy to the head and neck. In a study of patients with chronic obstructive pulmonary disease unrelated to cancer, Korkut et al. (2021) found that oral care with black mulberry syrup accelerated the

healing of oral mucositis caused by treatment and alleviated symptoms associated with mucositis. Contrary to these studies, Harman et al. (2019) and Sari et al. (2022) found that black mulberry syrup had no effect in preventing oral mucositis in patients undergoing stem cell transplantation or in patients who received radiation therapy for head and neck cancer, respectively.

Purpose

The purpose of this study was to determine whether black mulberry extract is an effective treatment for oral mucositis, dry mouth, and weight gain for patients with cancer as compared to sodium bicarbonate.

Methods

Design

This pilot study used a randomized quantitative study design. Institutional permission for the study was obtained from Tekirdağ Namık Kemal University Hospital in Turkey, and the study was approved by the Kayseri City Hospital Clinical Research Ethics Committee. Patients who agreed to participate were informed about the study purpose and process, and their written and verbal informed consent was obtained.

Sample and Setting

The study was conducted at Tekirdağ Namık Kemal University Hospital from August 11, 2021, to August 2, 2022. The sample consisted of 40 patients receiving chemotherapy on a 30-bed oncology unit. Patients with no or insufficient oral intake were excluded. According to guidelines from the European Society for Clinical Nutrition and Metabolism (Arends et al., 2017), inadequate oral intake is defined as not eating for more than one week, or an estimated energy intake of less than 60% of the need for more than one to two weeks, and associated weight loss. The inclusion criteria for this study were as follows: (a) inpatients on the oncology unit aged 18 years or older who were receiving their first course of chemotherapy treatment with methotrexate; (b) ability to speak and understand Turkish; (c) mobility; (d) no detected metastasis or diabetes mellitus, chronic renal failure, or acute renal failure; (e) adequate oral intake and intact oral mucosa prior to starting chemotherapy; and (f) no smoking or alcohol consumption. The dose for methotrexate was 3.5 g/m², with the first 0.5 g/m² administered in 1,000 ml 0.9% sodium chloride over 15 minutes and the remaining 3 g/m² administered over three hours. Oral mucositis, which is one of the common side effects of most antineoplastic agents, occurs most frequently because of treatment with methotrexate chemotherapy (Beşirik & Şahiner, 2018; Garrocho-Rangel et al., 2018).

Procedures

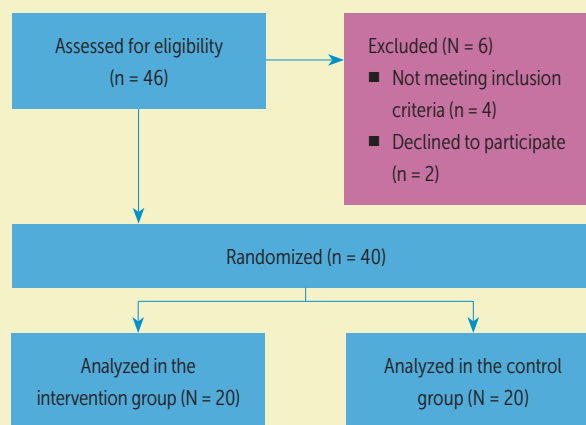
According to CONSORT (Consolidated Standards of Reporting Trials) (see Figure 1), patients who met the inclusion criteria were

allocated to the control group (N = 20), which received sodium bicarbonate, or the intervention group (N = 20), which received black mulberry extract. A total of 40 patients were included in the study to meet the parametric test assumptions ($\alpha = 0.05$, $\beta = 0.1$, $1-\beta = 0.9$). Patients were stratified according to gender, age, body mass index, and cancer type.

Prior to the intervention, oral mucositis, dry mouth, and weight were assessed in both groups. Oral care was applied by the nurse researcher to patients in the control group as 10 cc of 8.4% sodium bicarbonate mouthwash for 30 seconds three times per day for 15 days. For patients in the intervention group, oral care was applied by the nurse researcher for 60 seconds three times per day for 15 days using 5 ml of black mulberry extract, which contained ripe black mulberry fruit, citric acid, and about 9% fruit sugar. The extract used in this study was obtained using a cold infusion method and did not contain glucose or preservatives. With this method, a syrup is made by extracting black mulberry fruits. Patients were advised not to eat anything within 15–20 minutes of the application to avoid interfering with the mucosal lining (see Figure 2). Black mulberry extract has been approved by the Turkish Ministry of Agriculture and Rural Affairs.

Patients were assessed for oral mucositis and dry mouth, and weight was monitored at the following three time points: days 1, 7, and 15 of follow-up after oral application with sodium bicarbonate or black mulberry extract. A digital precision scale was used to measure each patient's weight. For consistency, patients were weighed while wearing the same clothes at 7 am at each of the three time points. The nurse researcher conducted the assessments.

FIGURE 1.
CONSORT FLOW DIAGRAM



CONSORT—Consolidated Standards of Reporting Trials

Data Collection

Data were collected using a descriptive characteristics form, the Oral Assessment Guide, the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring Schema, and a weight tracking form.

DESCRIPTIVE CHARACTERISTICS FORM: Based on the literature, a descriptive characteristics form was prepared by the researchers (Estfan et al., 2005; Zucca et al., 2015). The form consisted of six questions regarding patients’ gender, age, marital status, occupation, education level, and body mass index.

ORAL ASSESSMENT GUIDE: Oral mucositis was evaluated using the Oral Assessment Guide, which was first developed by Eilers et al. (1988) for use in adult patients and later revised. The original tool consists of five categories: lips, mucous membranes and tongue, gums, teeth, and saliva. In the revised tool, the mucous membranes category was divided into three parts (cheek, palate, and lip), and the teeth and dental prosthesis category was removed from the tool to reflect the severity of oral mucositis more accurately. Each category of the Oral Assessment Guide is scored on a scale ranging from 1 to 3,

“Oral mucositis decreased and weight gain increased at all three follow-up time points.”

and scores are categorized as follows: 5 points = no risk, 6–10 points = moderate risk, and 11–15 points = high risk. Total scores range from 8 to 24, with higher scores indicating a greater risk of developing mucositis. A Turkish study was conducted by Palloğ and Şendir (2018) to determine validity and reliability, and the Cronbach’s alpha was found to be 0.71.

RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEMA: Dry mouth was evaluated using the RTOG/EORTC Late Radiation Morbidity Scoring Schema. Total scores range from 0 to 5 points (0 = no dry mouth, 1 = mild dry mouth, 2 = moderate dry mouth, 3 = completely dry mouth, 4 = fibrosis, and 5 = late side effects directly related to death) (RTOG, 1999).

WEIGHT TRACKING FORM: The weight tracking form was prepared by the researchers in line with the literature (Del Fabbro et al., 2017; Leelasawatsuk et al., 2022). Weight was calculated in kilograms, and patients’ weights were recorded on the form at each follow-up time point.

FIGURE 2.

BLACK MULBERRY EXTRACT: SELECTED PROFILE BASED ON ACCESS AND AVAILABILITY IN THE UNITED STATES

SELECTED PROFILE

- Source: plant from the Moraceae family; native to southwestern Asia and the Iberian Peninsula
- Equivalent terms: *Morera negra*, *Morus nigra*, mulberry, murier noir, purple mulberry
- Extract properties: Ripe fruit contains malic and citric acid (about 9% sugar).
 - Black mulberry syrup used in the current study was extracted using cold fusion (pressing) method.
 - Advantages: Mulberry essence does not lose its nutritional value as it does with boiling methods; does not contain glucose or preservatives
- Formulations of extract available as capsules, leaf extract, syrup, fruit snack, and juice
 - Can be purchased by U.S. residents through various online retailers, pharmacies, and grocery stores
- Side effects and contraindications include pregnancy, breastfeeding, allergies, diabetes, and poor liver function.
- Medications that may be affected include lovastatin, ketoconazole, triazolam, and diabetes medications, among others.

Note. Based on information from Doğan et al., 2017; Lim & Choi, 2019; Sari et al., 2022.

Data Analysis

Descriptive statistics were used to characterize the data. Mean scores were used to compare outcomes between the two groups. Differences in repeated measures were calculated using the Mann–Whitney U test and Pearson correlation coefficients, with the error level set at $p = 0.05$.

Results

The demographic and clinical characteristics of the study sample are presented in Table 1. Characteristics were similar across the two groups.

The distribution of mean scores on the Oral Assessment Guide and the RTOG/EORTC Late Radiation Morbidity Scoring Schema for patients in the control (sodium bicarbonate) and intervention (black mulberry extract) groups at each time point (days 1, 7, and 15) is presented in Table 2. In both groups, there was a statistically significant decrease in mean scores on the Oral Assessment Guide on days 1, 7, and 15 of follow-up ($p = 0.001$). When comparing the two groups on days 7 and 15, mean scores in the intervention group indicated a statistically

significant decrease compared to scores in the control group ($p < 0.005$).

Mean scores on the RTOG/EORTC of patients in the control and intervention groups also showed a statistically significant decrease on days 1, 7, and 15 of follow-up ($p = 0.001$). When comparing the two groups on days 7 and 15, mean scores on the RTOG/EORTC in the intervention group were found to be lower than scores of patients in the control group ($p = 0.001$), which was statistically significant.

Regarding weight gain, the difference among kilogram measurements for all patients in the control group at all follow-up time points (days 1, 7, and 15) was statistically significant ($p = 0.001$), whereas no difference was found in measurements of the control group ($p = 0.618$). When comparing the two groups on days 7 and 15, it was determined that the weight gain of the patients in the intervention group was significantly higher than that of patients in the control group ($p = 0.01$).

Pearson correlation coefficients were calculated based on mean scores from all follow-up time points to establish the relationship between oral mucositis and dry mouth for both groups. For the control group, there was a moderate and statistically significant relationship found between the Oral Assessment Guide and the RTOG/EORTC Late Radiation Morbidity Scoring Schema ($r = 0.57$, $p = 0.001$). The relationship between the Oral Assessment Guide and the RTOG/EORTC Late Radiation Morbidity Scoring Schema in the intervention group was also statistically significant ($r = 0.875$, $p = 0.001$).

Discussion

Based on the results of this study, oral mucositis and dry mouth significantly improved in both groups on days 1, 7, and 15 after application of oral care. However, mean scores were statistically lower in the intervention group in which black mulberry extract was used, indicating that oral care with black mulberry extract was more effective than sodium bicarbonate in reducing oral mucositis and dry mouth. In their study of patients with head and neck cancer undergoing radiation therapy, Doğan et al. (2017) reported that black mulberry molasses prevented oral mucositis by 38% in study participants, delayed the formation of mucositis, and reduced the severity of mucositis. The current study showed similar results, indicating that black mulberry extract may be helpful in alleviating symptoms of oral mucositis and dry mouth following chemotherapy.

In their study of patients with head and neck cancer undergoing radiation therapy, Sari et al. (2022) investigated the effects of grape and black mulberry molasses as a treatment to prevent radiation therapy-induced oral mucositis and improve quality of life. The results indicated that although grape and black mulberry molasses improved patients' quality of life, they were not effective in preventing mucositis (Sari et al., 2022). For a sample of patients undergoing stem cell transplantation, Harman et al. (2019)

compared the effects of a chlorhexidine gluconate and benzydamine hydrochloride solution, a calcium and phosphate solution, and black mulberry syrup on oral mucositis and found that these

TABLE 1.
PATIENT CHARACTERISTICS BY GROUP

CHARACTERISTIC	CONTROL (N = 20)	INTERVENTION (N = 20)
	n	n
Age (years)		
20–40	5	8
41–59	8	6
60 or older	7	6
Body mass index (kg/m²)		
18.5–24.99	10	9
25–29.99	10	11
Cancer type		
Acute myeloid leukemia	6	6
Aplastic anemia	4	4
Acute lymphoblastic leukemia	2	2
Chronic lymphocytic leukemia	2	2
Multiple myeloma	2	2
Non-Hodgkin lymphoma	2	2
Breast	1	1
Lung	1	1
Education status		
Completed primary school	4	5
Completed middle school	9	9
Completed high school	7	6
Gender		
Female	9	11
Male	11	9
Marital status		
Married	15	16
Single	5	4

solutions prevented oral mucositis, which differs from the results of the current study (Harman et al., 2019; Sari et al., 2022).

Results from the current study suggest that oral care with sodium bicarbonate while undergoing treatment with chemotherapy was effective in preventing mucositis. In a study by Mohammadi et al. (2022), results indicated that the use of zinc chloride and sodium bicarbonate was effective in the treatment of oral mucositis in patients with cancer receiving chemotherapy, reducing oral mucositis severity and subsequently improving quality of life. Although not directly related to the results of the current study, the study by Yang et al. (2017) suggested that the use of 3% sodium bicarbonate in oral care was effective in preventing oral candidiasis. Yet, these results (Yang et al., 2017), as well as the results of Mohammadi et al. (2022), differ from those of the current study.

Although previous studies have evaluated the effectiveness of black mulberry extract and sodium bicarbonate on oral mucositis, their effects on dry mouth and weight gain have not been established. Based on the results of this study, oral mucositis decreased and weight gain increased at all three follow-up time points for the

intervention group. These results are similar to those of previous studies. For example, in a study of patients with myeloid leukemia, Pour-Fard-Pachekenari et al. (2019) reported that honey mouth-wash included in oral care was an effective treatment to prevent or reduce mucositis severity and encouraged some weight gain. Likewise, in their study on patients with head and neck malignancies, Co et al. (2016) found that honey added to oral care resulted in patient weight gain and increased oral food intake.

Limitations

This study had several limitations. The study was conducted at a single center, which contributed to the small sample size and limited generalizability. Complete randomization also could not be achieved because of the individual and physiologic characteristics of the patients included in the study.

Implications for Nursing

Results from this study suggest that black mulberry extract may be effective in preventing or reducing mucositis for patients receiving chemotherapy and may also support weight gain. Data

TABLE 2. DISTRIBUTION OF MEAN SCORES ON ORAL HEALTH MEASURES BY FOLLOW-UP TIME POINT

TIME POINT	CONTROL (N = 20)				INTERVENTION (N = 20)				MANN-WHITNEY U
	\bar{X}	SD	RANGE	p	\bar{X}	SD	RANGE	p	
Oral Assessment Guide				0.001*				0.001*	
Day 1	2.06	0.38	1-3	-	1.92	0.45	1-3	-	0.431
Day 7	1.9	0.27	1-3	-	1.53	0.32	1-3	-	0.003*
Day 15	1.77	0.76	1-3	-	1.21	0.21	1-3	-	0.004*
RTOG/EORTC				0.001*				0.001*	
Day 1	2.45	0.75	0-3	-	2.18	0.5	0-3	-	0.249
Day 7	2.05	0.51	1-3	-	1.31	0.71	0-2	-	0.001*
Day 15	1.55	0.51	1-2	-	0.54	0.03	0-1	-	0.001*
Weight (kg)				0.618				0.001*	
Day 1	68.55	12.03	-	-	65	8.97	-	-	0.043
Day 7	68.47	12.54	-	-	65.3	8.79	-	-	0.024
Day 15	68.76	12.51	-	-	66.7	7.98	-	-	0.004*

* p < 0.005 indicated statistical significance.

EORTC—European Organisation for Research and Treatment of Cancer; RTOG—Radiation Therapy Oncology Group

Note. The control group received oral care with sodium bicarbonate, and the intervention group received oral care with black mulberry extract.

Note. Oral health was measured using the Oral Assessment Guide (oral mucositis) and the RTOG/EORTC Late Radiation Morbidity Scoring Schema (dry mouth). Total scores on the Oral Assessment Guide range from 8 to 24, with higher scores indicating greater risk of developing mucositis. Total scores on the RTOG/EORTC Late Radiation Morbidity Scoring Schema range from 0 (no side effects) to 5 (side effects directly related to death).

from this randomized controlled intervention study allow for clinical evaluation of treatment effectiveness, contributing to an evidence-based foundation for clinical practice. The use of randomization and control and intervention groups in clinical practice increases the reliability of the study.

In the clinical oncology setting, nurses can evaluate the use and application of black mulberry extract and provide patient education. It is important to educate nurses and raise awareness about the use and importance of black mulberry extract in symptom management for patients with cancer. For this reason, it is believed that recommending black mulberry extract to patients and their families for managing symptoms of oral mucositis and dry mouth, and continuing to apply it when they are discharged, can be effective in symptom control.

Based on the results of this study, black mulberry extract can be a cost-effective and easily accessible complementary, non-pharmacologic treatment to prevent or reduce mucositis. The use of nonpharmacologic methods can be beneficial for the prevention of oral mucositis and dry mouth, which are undesirable symptoms caused by chemotherapy. Clinical oncology nursing can support patients by providing cost-effective, evidence-based options to prevent mucositis associated with chemotherapy administration.

Conclusion

This randomized pilot study evaluated the effects of oral care with black mulberry extract compared to sodium bicarbonate on oral mucositis, dry mouth, and weight gain in patients with cancer undergoing chemotherapy. The results suggest that oral care with black mulberry extract can be an effective treatment for mucositis and dry mouth. In addition, black mulberry extract may be a more effective treatment for oral mucositis compared to sodium bicarbonate. Study results also suggest that patients who use black mulberry extract may see increases in weight gain.

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IMPLICATIONS FOR PRACTICE

- Educate patients about the potential benefits of complementary and nonpharmacologic treatments for symptom management.
- Consider oral care with black mulberry extract to alleviate oral mucositis and dry mouth in patients receiving chemotherapy.
- Support patients by providing cost-effective, evidence-based options to prevent oral mucositis caused by chemotherapy.

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EDITOR'S NOTE

Herbal remedies and supplements are widely used for a variety of conditions and symptoms, including cancer or cancer treatment–related symptoms and side effects (National Cancer Institute, 2022). Worldwide, there are various approaches to regulate herbals used as treatments to ensure their safety and effectiveness. In the United States, herbals used as treatment are not regulated by the U.S. Food and Drug Administration (2007) and do not adhere to consistent standards from other regulatory entities. Criteria or claims to establish safety and effectiveness typically originate with the manufacturer.

This study, which evaluated the effectiveness of black mulberry extract as a treatment for oral mucositis and dry mouth, is an example of a clinically based study led by nurses in Turkey. Results from this study add data and clinical experience to a clinical knowledge base about herbal remedies used in the oncology setting. Clinical studies like this study can support potential effective treatments for side effects associated with cancer and treatment. Yet, as a reminder, this herbal-based treatment to prevent or limit mucositis and dry mouth associated with cancer treatment has not been tested or approved in the United States, so any U.S.-based regulatory standards to confirm safety or effectiveness cannot be applied.

As with any treatment–regulated or unregulated—oncology nurses in their role as educators can provide patients and caregivers with data-based information, a context for safety and effectiveness, and a clinical perspective about treatment expectations (Oncology Nursing Society, 2020).