

# Evaluation the effect of grape seed extract (GSE) on oral mucositis in patients with head and neck radiotherapy history

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## Research Article

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# Abstract

**Introduction:** Mucositis is one of the most important complication of radiotherapy. Some factors such as type of treatment and degree of patients sensitivity effect on mucositis occurrence. This research was implemented to evaluate the effect of grape seed extract on radiation induced mucositis.

**Method and material:** This research is a double blinded randomized clinical trial implemented on 78 patients undergoing head and neck radiotherapy in oncology and radiotherapy ward of Imam Reza hospital of Tabriz. The patients were randomly divided in two groups, intervention and control group. Each group included 39 patients. Intervention group used 2% grape seed extract mouthwashes and control group used placebo mouthwashes. The mouthwashes were used 3 times a day for 2 weeks. In order to statistical analyze of collected data, spss 20 software was applied.

**Results:** The results showed that according to Friedman test, on 10<sup>th</sup> and 14<sup>th</sup> days mucositis grade and incidence had a significant difference between intervention and control groups.

**Conclusion:** The study findings indicated that grape seed extract mouthwash in preventing radiation induced mucositis was more effective than placebo. Thus this agent can be recommended as an appropriate medicine in order to eliminate oral mucositis symptoms.

## Introduction

Nowadays, Cancers are one of the most important health challenges. according to the World Health Organization, diagnosis of cancer is increasing steadily all around the world(1). To treat cancer, various methods are used, including radiation therapy and chemotherapy(2) which are systemic methods and have the greatest effect on tumors with rapid growth(3). One of the potential toxic effects of radiotherapy is oral mucositis or the inflammatory response of oral tissues(4). Oral mucositis refers to the mucosal lesions of the oral cavity and the functional problems that result from them(5). Patients who receive combination chemotherapy or radiotherapy for head and neck tumors, or patients who receive high-dose chemotherapy before a bone marrow transplant, usually experience more severe oral mucositis. Studies have shown that between 33% and 51% of patients receiving standard chemotherapy protocols develop this acute complication(6). Antibodies and anti-tumor antibiotics are the main causes of mucositis(7). Disruption of the epithelial phase of cells has been implicated(8). Factors such as the type of treatment and the degree of sensitivity of patients affect the incidence of oral mucositis(9, 10). These painful lesions cause problems with food intake and oral hygiene, increase the risk of local and systemic infections, as a result, the amount of chemotherapy is limited or stopped(11). Specific radiotherapy methods with similar cytotoxic potency have different destructive effects on the oral mucosa of patients. However, the mechanism of radiation-induced mucosal damage and how these drugs work have not been fully elucidated. On the other hand, information about the toxicity of some drugs differs in different studies. Many studies have shown that cytotoxic substances and anti-metabolite and alkylating drugs are associated with the occurrence and severity of oral mucositis(12, 13). The study by Wong et al. also

showed that oral mucositis was higher in patients treated with cytotoxic drugs and alkylating agents(14). Malet-Martino et al. Showed that patients with hematologic malignancies were at higher risk of developing severe oral mucositis than those with solid tumors(15). An important part of the role of malignancies in the formation of mucositis seems to be due to differences in their chemotherapy regimen and the prescribed dose of the drug, not the disease itself(16). Also, the relationship between patients' sex and the incidence of oral mucositis has been ruled out by some studies(17, 18). Although no definitive method has yet been proven to treat and prevent oral mucositis, various measures are currently being proposed, including oral hygiene, various mouthwashes, and local anesthetics such as lidocaine, magnesium-containing antacids, diphenhydramine, nystatin, sucralfate, and psychotherapy(8). however, these treatments sometimes cause side effects either(19). the role of normal oral flora in oral mucosa is not fully understood. Eliminating potential sources of oral infection, such as gingivitis, caries, or dental plaque, appears to be effective in reducing the risk of mucositis(20).

For the treatment of any primary disease, a complete knowledge of the disease and the factors affecting it is required. Oral cancer, like other cancers, is caused by mutations, activations or amplifications of proto-oncogenes and tumor suppressor genes, as well as a loss of cell cycle control (Over proliferation) and cell survival (less than normal apoptosis) occurs(21). Past studies have shown that grape seed extract has preventive and inhibitory properties against breast, lung, skin, prostate, stomach and intestinal cancers(22). Grape tree belongs to the family Vitis Vinifera, genus Ampelidaceae, genus Vitis, subgenus Euvitis and Iranian grape species(23). Grape seeds and skin are used in traditional medicine and its fruit as a dietary supplement. On the other hand, grape seed extract increases the growth and survival of macrophage cells, heart and skin(24). Grapes contain active ingredients such as flavonoids, polyphenols, anthocyanins, proanthocyanidins and procyanidins .These biologically active compounds have cytotoxic, anticancer and antimicrobial effects by interfering with various biological pathways (25). The proanthocyanidin in grape seed extract is responsible for its antioxidant, anti-inflammatory, anti-fungal, anti-bacterial and anti-allergic activities(26). Proanthocyanidins(PCO) It is a type of bioflavonoid and a very powerful antioxidant that can prevent cell damage caused by free radicals, repair and strengthen connective tissues and help the activity of enzymes(27). Antioxidants are substances that, when present in food or in the body, even in very small amounts, protect the body against a variety of oxidative damage that may be caused by reactive oxygen species(28). According to existing studies, the antioxidant power of proanthocyanidins is 20 times higher than vitamin E and 50 times higher than vitamin C(29). Since cell damage and lipid peroxidation, one of the most prominent oxidative damage, occurs primarily in tissues, and grape seed extract as an oxidizing agent is one of the defense lines in these cell sites; it can be hypothesized that grape seed extract as the most important anti-oxidant can be effective in neutralizing free radicals in order to strengthen the cellular anti-oxidant system and improve performance and time to exhaustion by preventing increased lipid peroxidation(30). Olaku et al. In a systematic study investigating the role of grape seed extract in the treatment of radiation therapy toxicity showed that both types of extract (GSE grape seed extract and GSP grape skin extract) reduce the cytotoxic effects of chemotherapy or radiation therapy on normal cells(31).

Considering that it seems that no study has been done to evaluate the effect of grape seed extract and its compounds on oral mucositis, the present study was performed to investigate the effect of grape seed extract on oral mucositis in patients with a history of radiotherapy.

## Material And Methods

The protocol of the clinical trial which was conducted according to the ethical principles of Helsinki (version 2002), was approved by the ethics committee of Tabriz University of Medical Sciences) IR.TBZMED.REC.1397.515(. This randomized controlled double-blind clinical trial study was performed from November 2018 to May 2019 on 78 hospitalized patients undergoing radiotherapy to the oncology ward of Imam Reza Hospital who have the characteristics of the units under study.

Power & sample size software was used to determine the sample size. The formula for calculating the sample size to test the difference between the two means in the two groups is:

$$n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times pq / (p_1 - p_2)^2$$

(For test studies, the ratio of a qualitative trait in two different populations) was used, which considering  $\alpha = 0.05$ , power 80% and p and q equal to 50% and mucosal incidence was estimated to be 30% for the intervention group and p1 = 60% for the control group and 29 patients with a 10% error for each group.

These participants were randomly divided into control (n = 39) and intervention (n = 39) groups. The patients who were full consciousness with oral mucosal health and receiving radiation at a rate of at least 60 grey and the dose received per session is 200 cGy. The participants should not have respiratory diseases and asthma, diabetes, autoimmune diseases and fever and neutropenia. They also should not use another mouthwash solution during the research and receive other combined treatment such as chemotherapy. Consuming antibiotics and painkillers continuously during the study was forbidden. The patients should not be drug addict either. The participant, who met inclusion and exclusion criteria, were enrolled in this evaluation, if they signed the written consent form.

## Collection Tools

The tools of this study included a two-part questionnaire and a checklist to determine the severity of oral mucositis. The first part of the questionnaire was demographic information including age, gender, educational status, and body mass index. The second part of the questionnaire included questions about smoking history, drugs, history of oral and dental complications, history of oral mucositis, duration of disease, radiotherapy area, daily radiation dose and total radiation dose. The questionnaire was completed through interviews and the patient's medical record.

The checklist included: Determining the severity of oral mucositis according to the 2005 World Health Organization standard, which divides oral mucosa into five distinct degrees (0–4). This instrument was

used to evaluate the condition of oral mucosa, incidence and degree of oral mucosa before and after the intervention. Pain, comfort of mouthwash, sleep and dry mouth were also measured during follow-up.

A VAS ruler was used to measure the amount of pain.

The Short-form Vision (SXI-D) criterion was used to measure dry mouth (Xestomia) and the patient was asked 5 questions and according to the answers given, the scores are given. A score of 5 meant no Xestomia and a score of 15 meant the most severe state of Xestomia. Dry mouth status was assessed as spectral, without dry mouth, very low, low, moderate, very high.

Sleep status was assessed as a spectrum: comfortable sleep, occasional awakening, continuous awakening and, more often, sleep disturbance.

Checklist observations were performed simultaneously by two observers and the agreement coefficient between the two observers was determined.

## How To Intervene

In the intervention group, mouthwash with grape seed essence (mouthwash of 2% grape seed extract, prepared in the Pharmaceutical Research Center of Tabriz University of Medical Sciences) and in the control group placebo mouthwash (96% solution of distilled water and colorant) prescribed. Patients in both groups were taught how to use mouthwashes. The plan was to use mouthwash three times a day after breakfast, after lunch and before going to bed after brushing, each time 5 ml of mouthwash was used for 3 minutes. Patients used prescribed mouthwashes from the first day of radiotherapy to the fourteenth day after starting radiotherapy. The condition of the oral mucosa of the subjects was examined in these 14 days and followed up (during treatment, after discharge at home and time of return). During the implementation, due to its double-blind research method, the researcher and the research units were unaware of the nature of mouthwashes.

Data has been analyzed by SPSS version 20. The data obtained from the study were expressed descriptively (frequency, mean, median and deviation). Friedman test was used to compare the degree of mucositis at different times in the two groups and It was seen that there is a difference between them. ( $p < 0.001$ )

Khi-deux test was used to evaluate the relationship between the degree of mucositis in the first-fifth-tenth-fourteenth days after using mouthwash between patients in the control and intervention groups. dry mouth, sleep quality and ease of use of the solution in four time periods between patients in the two groups also was performed by this method.

## Results

This study is a clinical trial and 78 samples were included in the study, of which 39 samples were in the intervention group, which were statistically analyzed as group A, and 39 samples in the control group, which are introduced as group B. In this study, 40 patients (51.3%) were male and 38 patients (48.7%) were female, who were equally divided into groups A and B.

The age of participants in interview group was  $48/15 \pm 66/48$  and  $36/19 \pm 84/51$  in control group. (Table4-1)

Table 4.1  
Descriptive Statistics of demographic characteristics, history of systemic disease, smoking, drug and alcohol use, radiation dose, radiation time

	Intervention Control		p-value
	Mean (standard deviation)		
Age	48.66(15.48)	51.84(19.36)	0.426
Radiation dose	6392.31(1271.01)	6923.07(1886.16)	0.149
Radiation time	25.58(6.23)	25.38(6.21)	0.855
Frequency (percentage)			
History of systemic disease	No	34(87.2)	0.745
	Yes	5(12.8)	
Use drugs	No	36(92.3)	0.5
	Yes	3(7.7) 2(5.1)	

67 (85.9%) had no history of systemic disease and only 11 (14.1%) had systemic disease, which showed no statistically significant difference between the two groups ( $P = 0.745$ ). Smoking was also observed in 22 (28.2%) patients, which was divided equally between the two groups (11 smokers in each group) and had a non-significant difference ( $P = 0.999$ ). Also, drug use was reported only in 5 (6.4%) people, which was a non-significant difference between the two groups ( $P = 0.5$ ). These patients had only a history of drug use and had stopped using drugs 6 months ago.. In none of the patients chemotherapy was combined with radiotherapy, and in case they receive chemotherapy at the same time they were excluded from the study. Also none of the patients had mucositis before entering the study. Evaluation of mucositis, dry mouth, pain, sleep pattern and comfort in using mouthwash on days 1, 5, 10 and 14 after using mouthwash between patients in the two groups was performed by khi-deux test and the results are shown in Tables 4 - 2 to 4-6.

Table 4.2  
Comparison of mucosal grade in two groups at different times

Degree of mucositis groups		Review days			
		1	5	10	14
Absence of mucositis	control	39(100)	30(76.9)	18(46.2)	13(33.3)
	intervention	39(100)	33(84.6)	27(69.2)	26(66.7)
Feeling of burning, erythema and redness (grade 1)	control	0	9(23.1)	15(38.5)	7(17.9)
	intervention	0	6(15.4)	11(28.2)	10(25.6)
Local erythema and ulcers and inability to swallow hard foods (grade 2)	control	0	0	6(15.4)	19(48.7)
	intervention	0	0	1(2.6)	3(7.7)
Wounds with diffuse erythema and inability to swallow (grade 3)	control	0	0	0	0
	intervention	0	0	0	0
Progression of the mucosa to the extent that nourishment is possible (Grade 4)	control	0	0	0	0
	intervention	0	0	0	0

During the study, patients showed no mucosal disease on the first day. On the 5th day, 33 (84.6%) patients in the intervention group and 30 (76.9%) patients in the control group (placebo) were without mucositis. At this time, 6 (15.4%) people in the intervention group and 9 (23.1%) people in the control group had burning sensation and red erythema (grade1 mucositis). This degree of mucositis at 5 days did not cause a statistically significant difference between the two groups ( $P = 0.389$ ). On the 10th day, 27 (69.2%) patients in the intervention group and 18 (46.2%) patients in the control group did not have mucositis and only 1 (2.6%) in the intervention group and 6 (15.4%) in the control group had local erythema and ulcers and inability to swallow solid foods (grade 2 mucositis). At this time, there was a significant relationship between amount of mucositis in the two groups ( $P = 0.05$ ). On day 14, 3 (7.7%) in the intervention group and 19 (48.7%) in the control group had local erythema and ulcers and inability to swallow solid foods (grade 2 mucositis). There was a statistically significant difference between the two groups ( $P < 0.001$ ).

Differences between mucositis at different times were also compared by Friedman test and the result showed that there was a difference between different times in terms of different stages of mucositis ( $P < 0.001$ ).

Table 4.3  
Comparison of dry mouth in two groups at different times

Intensity of dry mouth groups		Review days			
		15	10	14	14
No dry mouth	control	39(100)	25(64.1)	13(33.3)	11(28.2)
	intervention	39(100)	32(82.1)	22(56.4)	13(33.3)
Very mild	control	0	8(20.5)	9(23.1)	3(7.7)
	intervention	0	7(17.9)	16(41)	20(51.3)
mild	control	0	6(15.4)	7(17.9)	11(28.2)
	intervention	0	0	1(2.6)	6(15.4)
moderate	control	0	0	9(23.1)	12(30.8)
	intervention	0	0	0	0
severe	control	0	0	0	0
	intervention	0	0	0	0

The study of dry mouth showed that in the intervention group in the first days all the patients had no dry mouth, on the 5th, 10th, 14th day, 82.1%,56.4%,33.3% had no dry mouth respectively. In control group all the patients had no dry mouth too. on the 5th, 10th, 14th day, 64.1%, 33.3%, 28.2% had no dry mouth respectively. According to Friedman test, in both groups, there was a change in the severity of dry mouth over time ( $P < 0.001$ ). On the first day, all patients had no dry mouth and the two groups were similar. But on the fifth day ( $P = 0.031$ ), the tenth day ( $P = 0.001$ ) and the fourteenth ( $P = 0.001$ ), the intervention group had less dry mouth than the control group.

Table 4.4  
Comparison of pain in two groups at different times

Intensity of pain groups		Review days			
		15	10	14	
Without pain	control	39(100)	24(61.5)	11(28.2)	10(25.6)
	intervention	39(100)	27(69.2)	19(48.7)	8(20.5)
Pain degree 1	control	0	3(7.7)	4(10.3)	3(7.7)
	intervention	0	8(20.5)	13(33.3)	19(48.7)
Pain degree 2	control	0	12(30.8)	10(25.6)	5(12.8)
	intervention	0	4(10.3)	6(15.4)	10(25.6)
Pain degree 3	control	0	0	7(17.9)	10(25.6)
	intervention	0	0	1(2.6)	2(5.1)
Pain degree 4	control	0	0	7(17.9)	11(28.2)
	intervention	0	0	0	0

On the first day, all the patients of both group had no pain. But in intervention group, on the fifth day 69.2%, on the tenth day 48.7% and on the fourteenth day 20.5% had no pain and in control group, 61.5% on the fifth day, 28.2% on the tenth day and 25.6% on the fourteenth day had no pain. According to Friedman test, there was a change in pain in both groups over time ( $P < 0.001$ ). on the fifth ( $P = 0.04$ ), tenth ( $P = 0.001$ ) fourteenth day ( $P = 0.001$ ), the intervention group had less pain than the control group.

Table 4.5  
Comparison of sleep status in two groups at different times

Sleep status groups		Review days			
		15	10	14	
Comfortable sleep	control	39(100)	37(94.9)	26(66.7)	17(43.6)
	intervention	39(100)	39(100)	35(89.7)	26(66.7)
Waking up occasionally	control	0	2(5.1)	13(33.3)	21(53.8)
	intervention	0	0	4(10.3)	13(33.3)
Waking up constantly	control	0	0	0	1(2.6)
	intervention	0	0	0	0
Sleep disturbance	control	0	0	0	0
	intervention	0	0	0	0

The study of sleep status showed that in the intervention group in the first and fifth days all patients had comfortable sleep, on the tenth day 89.7% and on the fourteenth day 66.7% had sleep. In the control group, all patients had comfortable sleep in the first days, 49.9% on the fifth day, 66.7% on the tenth day and 43.6% on the fourteenth day. According to Friedman test in both groups, there was a change in sleep status over time ( $P < 0.001$ ).

On the first and fifth days ( $P = 0.247$ ), the two groups were similar in terms of sleep status, but on the tenth ( $P = 0.014$ ) and fourteenth ( $P = 0.042$ ) days, the intervention group had a better sleep status than the control group.

Table 4.6  
Compare the convenience of using mouthwash in two groups at different times

Amount of convenience groups		Review days			
		15	10	14	14
Without problem	control	38(97.4)	38(97.4)	38(97.4)	38(97.4)
	intervention	31(79.5)	31(79.5)	31(79.5)	31(79.5)
Slight discomfort when consuming	control	1(2.6)	1(2.6)	1(2.6)	1(2.6)
	intervention	8(20.5)	7(17.9)	7(17.9)	7(17.9)
Severe discomfort when consuming	control	0	0	0	0
	intervention	0	1(2.6)	1(2.6)	1(2.6)
Impossible to consumption	control	0	0	0	0
	intervention	0	0	0	0

The convenience of using mouthwash showed that 79.5% of the patients in the intervention group and 97.4% of the patients in the control group had no problems in using mouthwash during the whole follow-up period (2 weeks). According to Friedman test in both groups, there was no change in the ease of using mouthwash over time. According to the Chi-square test, the two groups did not have a significant difference in the ease of using mouthwash on each of the follow-up days.

## Discussion

Radiation therapy has destructive effects on the oral mucosa of patients. One of the potentially toxic effects of radiation therapy is oral mucositis or the inflammatory response of oral tissues. But its mechanism has not been fully understood. Grape seed extract increases the body's antioxidant defense. The aim of this study was to evaluate the effect of grape seed extract on oral mucositis in patients with radiotherapy.

In the present study, the prevalence of oral mucositis in the intervention and control groups increased over time. The results showed that the prevalence of oral mucositis in the control and intervention groups increased from 0% on the first day to 66.7% in control group and 33.3% in intervention group after two weeks. The prevalence and severity of oral mucositis on the tenth and fourteenth day in the control group was significantly higher than the intervention group.

Olaku et al. (2015) in a systematic study showed that grape seed extract and grape skin extract both reduced the cytotoxic effects of chemotherapy or radiation therapy on normal cells(31).

Saleh et al. (2017) showed that grape extract and Cetuximab drugs both reduced inflammatory cells in the mucosa of mice, but grape seed extract also eliminated the toxic effects of Cetuximab. The results of these studies are consistent with the present study. In this study, after the time of radiotherapy when the symptoms of oral mucositis appear in people, there is a significant difference in patients using mouthwash containing grape seed extract and fewer people in comparison with control group had oral mucositis and also the severity of Mucositis was lower in the patients of this group(32).

Cheah et al. (2014) illustrated that grape seed extract is a new treatment option to reduce the signs and symptoms of intestinal mucositis while simultaneously affecting colon cancer cells(33).

One of the functions of anticancer drugs is to induce apoptosis and studies have shown that grape seed extract has preventive and inhibitory properties against cancer(34, 35). Dinicola et al. (2013) showed that grape seed extract had the ability to induce apoptosis on cancer cells from the internal pathway of apoptosis by increasing the intracellular concentration of calcium ions and producing reactive oxygen species (ROS) products(36).

Proanthocyanidin is a type of bioflavonoid and a very powerful antioxidant that can prevent cell damage caused by free radicals, repair and strengthen connective tissues and help the activity of enzymes. This substance reduces the amount of inflammation by reducing the production of histamine(28, 37, 38). Rodríguez et al. (2019) have demonstrated Grape seeds proanthocyanidins destroy free radicals more potently than vitamins C, E and  $\beta$ -carotene in vitro and in vivo(39).

In order to an important part of the role of malignancies in the formation of mucositis, in fact, is due to differences in their chemotherapy regimen and the prescribed dose of the drugs, not the disease itself(40), therefore, in the present study, both intervention and control groups were similar in terms of radiation dose and duration of radiation. In this study, some of the side effects of oral mucositis due to radiation therapy, such as dry mouth, pain due to oral mucositis, sleep status and ease of using mouthwash were investigated. The results showed that in both groups, dry mouth, the amount of pain and sleep status increased over time by enhancing oral mucositis during this time, but in the intervention group the status of these variables is more appropriate than the control group. So that on the tenth and fourteenth days, the amount of pain and dry mouth in the intervention group is less than the control group and sleep in the intervention group is better than the control group. Patients in both groups were comfortable in using mouthwashes and no significant difference was observed between the two groups.

The flavonoids in grape seed extract by applying antioxidant effects(41) can partially explain the analgesic effects of grape seed in this study. Nallathambi et al. (2020) showed grape seed extraction increased the expression of antioxidant enzymes significantly. grape seed extraction also enhanced the expression of stress-induced antioxidant genes (GSR, SOD1, SOD2, and GPX2). It can suppress the expression of pro-inflammatory cytokines and promote the expression of anti-inflammatory cytokines following LPS-induced inflammatory response. (28) Maintaining oral hygiene can reduce oral mucositis and delay the onset and duration of mucositis(42) .Therefore, considering the effective role of oral condition before starting chemotherapy and oral hygiene in the development of oral mucositis, it seems that eliminating potential sources of oral infection such as gingivitis, caries or dental plaque is efficient in reducing the risk of mucositis. Thus, advising patients to promote oral health before starting chemotherapy is recommended.

## Conclusion

Grapes seed extract mouthwash revealed proper therapeutic effect on severity and incidence of mucositis, dry mouth of patients, amount of pain and sleep comfort of them. In addition, it did not have side effects. It might be considered as new and safe traditional treatment option for trating mucositis. Further clinical studies based on gender and age groups and the use of other products containing grapes seed extract are recommended.

## Declarations

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### Conflicts of interest

There are no conflicts of interest.

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