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Original Research Article

Comparing the effects of saffron and Mucosamin® spray on oral mucositis induced by radiotherapy: A randomized controlled clinical trial

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Abstract

Objective: Mucositis is a common oral complication of the non-surgical therapy of cancer. Numerous studies have explored the pharmacological effects of saffron (Crocus sativus) in medicine. This study aimed to compare the effectiveness of saffron extract to Mucosamin® on relieving radiotherapy-induced oral mucositis.

Materials and Methods: This randomized controlled clinical trial was conducted on head and neck cancer patients who received radiotherapy treatment at the oncology clinic of Shahid Beheshti Hospital in Qom. A total of 68 patients were divided into two groups of 34. In addition to standard treatment, the first group received six puffs of brewed saffron spray (100 mg) daily, and the second group received six puffs of Mucosamin® for 4 weeks. Repeated measures ANOVA, T-test, and Chi-square test were utilized to analyze pain intensity and mucositis grading. All data were analyzed using SPSS version 22.

Results: The average pain intensity and mucositis grade decreased in both groups (a total of 61 patients). At baseline, the average pain intensity for the saffron and Mucosamin® groups was 6.29 ± 1.61 and 6.70 ± 1.93. By the end of the study, these figures dropped to 3.61 ± 1.35 and 4.00 ± 1.23. Likewise, the average mucositis grade in the two groups was 2.87 ± 0.34 and 2.56 ± 0.50 at the baseline, decreasing to 2.70 ± 0.46 and 2.40 ± 0.49 at the end of the study, respectively. There was no significant difference in the reduction of mucositis grade ($p= 0.246$) or pain intensity ($p= 0.38$) between the two groups.

Conclusion: The brewed saffron spray showed effectiveness comparable to Mucosamin® spray in reducing pain intensity and grading oral mucositis.

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Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide, with over 660,000 new cases and 325,000 deaths each year (Sung et al. 2021). Approximately 90% of HNCs are squamous cell carcinomas which develop from the epithelial lining of the oral cavity, pharynx, and larynx (Johnson et al. 2020). The primary treatment for HNC is radiotherapy which destroys cancerous tissue by disrupting cell survival and proliferation. Cells with high proliferation rates such as epithelial and endothelial cells, are particularly susceptible to radiation damage (Pfister et al. 2011). Rapid cell division in the oral cavity makes mucosal cells especially vulnerable to the adverse effects of radiation (Shih et al. 2003).

Oral mucositis (OM) is often painful and characterized by erythema or ulcers in the oral mucosa (Elting and Shih 2004). Studies show that OM commonly occurs in patients with HNC undergoing radiotherapy. In some cases, it may affect up to 100% of patients with HNC and is therefore considered a significant problem for this group (Maria, Eliopoulos and Muanza 2017). Pain associated with OM can lead to increased disability and, in some cases, the need for intravenous nutrition. If left untreated, OM can significantly increase the risk of secondary infections and reduce life expectancy (Shillingburg et al. 2017).

Based on clinical evidence, a variety of interventions are used to prevent or alleviate OM in cancer patients receiving head and neck radiotherapy. These include supportive care, pain management, oral anesthesia (such as lidocaine, and magnesium combined with antacids and diphenhydramine), laser therapy, and mouthwash. Recently, some clinical evidence supports ice-sucking and cryotherapy (Hong et al. 2019). Despite these options, there is currently no definitive treatment for OM.

Various preventive strategies have also been suggested, including the use of natural substances and herbal remedies which may work through different mechanisms (Rodrigues and Henriques 2017). In cases where stimulating saliva production with medication proves difficult, or where salivary gland damage is irreversible, saliva substitutes like Mucosamin®may be the only remaining option. Mucosamin® has lubricating and antibacterial properties (Łysik et al. 2019). In this respect, it can be an effective choice for relieving the symptoms of OM (Amaral et al. 2012; Halder et al. 2023; Lam-Ubol et al. 2021; Yarom et al. 2020). Mucosamin® consists of ingredients such as water, sodium hyaluronate, glycine, propylene glycol, lysine, leucine, and proline (Ruggiero et al. 2018).

The saffron plant, scientifically known as *Crocus sativus*, is a perennial species characterized by long, linear, green leaves resembling leeks, typically about 10 centimeters in length, which emerge directly from a robust underground bulb, known as the saffron tuber. The most valued part of this plant is the stigma of the saffron flower, recognized as one of the most potent natural antioxidants. Saffron contains safranal, beta-gamma-carotene, glucoside, crocin, crostin, volatile essential oils, lycopene, and picrocin (a type of glycoside) (Altinoz et al. 2015; Mzabri, Addi and Berrichi 2019). Saffron and its active components have several beneficial medical effects such as anti-inflammatory, anticonvulsant, antidepressant, anti-tumor, and radical-scavenging properties and learning, and memory improvement effects (Moshiri, Vahabzadeh and Hosseinzadeh 2015). Also, *in vitro* studies have shown that saffron is toxic to cancer cells such as gastrointestinal adenocarcinoma, and can inhibit carcinogenesis in rats (Abdullaev and Espinosa-Aguirre 2004).

Additionally, previous studies have highlighted saffron role in increasing cervical mucus secretion and promoting wound healing (Alemzadeh and Oryan

2018; Kashani et al. 2013). Besides, radiation oncologists sometimes prescribe artificial saliva to patients to alleviate OM (Amaral et al. 2012; Kang et al. 2017).

Despite the lack of studies on the effectiveness of saffron extract in treating radiotherapy-induced OM, the current study aims to accurately assess its impact on patients' quality of life and various treatment indicators, comparing its effects with those of mucosamin. Given concerns about potential tooth discoloration from saffron use, we monitored and compared the color of participants' teeth before and after the intervention.

Materials and Methods

Design

This randomized, double-blind research was conducted at Qom University of Medical Sciences, Qom, Iran (with the ethics code of IR.MUQ.REC.1401.229 and IRCT registration number IRCT20221207056743N1). The research was carried out over a six-month period in 2023 (From May to October) .

Participants

The patients were selected using the block randomization method. Based on findings from the study by Patil et al.(Patil et al. 2015) and considering the severity of OM in the two groups according to the World Health Organization (WHO) criteria, the sample size was calculated based on a mean difference of 0.6 ($\mu_1 = 2.0$, $\mu_2 = 2.6$), standard deviations of 0.9 and 0.5, a significance level (α) of 0.05, and a power ($1–\beta$) of 90%. Finally, 31 patients were included in each group. To account for potential dropouts during the study, a total of 34 patients were enrolled in each group.

During the study, six patients died (three from the saffron group and three from the Mucosamin® group). Additionally, one participant from the Mucosamin® group was excluded due to a lack of cooperation. Ultimately, the data from 61 patients were analyzed (Figure 1). All participants were informed about the trial conditions in accordance with clinical trial principles and ethical standards. The methods and procedures for patient selection, drug administration, and monitoring of side effects and outcomes adhered to the guidelines of Good Clinical Practice and the Helsinki Declaration. Furthermore, detailed information regarding the objectives of the study was provided to the participants, and their informed consent was obtained.

Inclusion and exclusion criteria

The inclusion criteria for this study were consent to participate in the trial , male and female patients aged 18-60 years, patients with head and neck cancers undergoing radiotherapy receiving at least 36 to 40 Gy of radiation (Elting and Shih 2004), at least four weeks having passed since the start of radiotherapy, no allergy to saffron, and no history of heart disease or blood pressure. Conversely, exclusion criteria included other oral and dental diseases, a history of long-term use of anticoagulant and antiplatelet drugs, pregnancy or breastfeeding, a history of diabetes or high blood pressure, autoimmune diseases, Graft-Versus-Host-Disease (GVHD), a history of salivary depressant drugs, alcohol consumption or drug addiction, a history of bone marrow transplantation, presence of active lesions, oral infections or mucosal ulcers before starting radiotherapy, reluctance to continue treatment, any surgery or trauma, or suffering from heart, liver or kidney failure, or any disease with manifestations similar to OM.

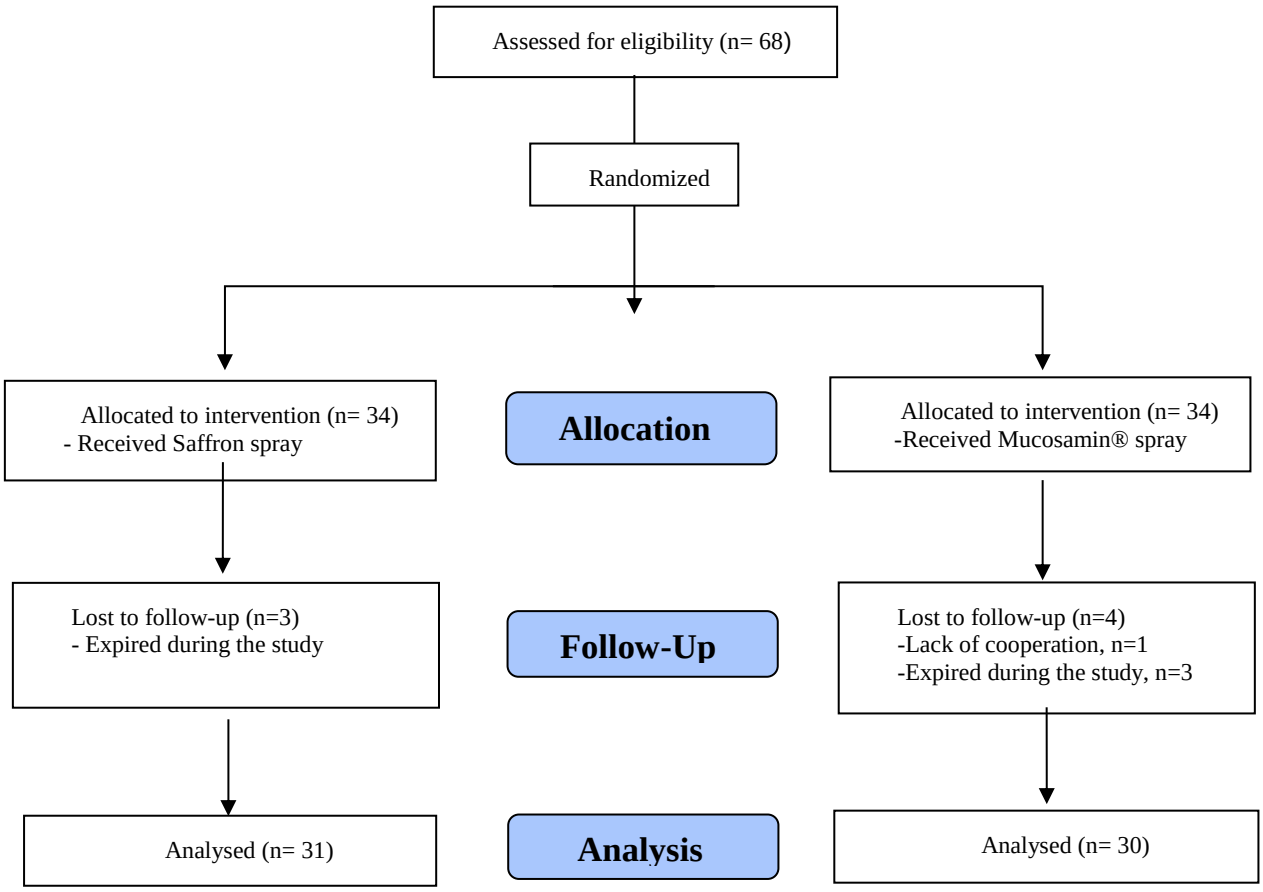

Figure 1. CONSORT Flow Diagram

Interventions

In this study, patients were randomly assigned to one of the two groups and received standard treatment such that:

Group 1: Patients in this group received conventional OM prevention treatments (e.g. pilocarpine and Cevimeline tablets) along with 3 puffs of a brewed saffron spray twice daily for 4 weeks. Each administration consisted of 6 puffs, providing 100 mg of saffron with a concentration of 1%. Patients were instructed not to rinse their mouths or eat for 30 min after using the spray.

Group 2: Patients in this group receive the same conventional OM treatments, as well as a Mucosamin® spray (Made by Biofarma company, a product of Professional Dietetics, Italy). The volume and dosage of the Mucosamin® spray were equivalent to those of Group 1.

Also, the results obtained for both groups before and immediately after the intervention were determined and compared regarding tooth color (using the Vita shade guide).

To prepare the brewed saffron spray, one gram of ground Qaenat saffron stigma was dissolved in 100 ml of distilled water at a temperature of 80°C. After 2 hr, the solution was filtered through several layers of filter paper. The shelf life of brewed saffron spray was 5 months, and it was stored properly in a dark, cool, and dry place (refrigerator).

To maintain blinding for both patients and the primary researcher, containers similar to those used for Mucosamin® were utilized for packaging the saffron spray. These bottles were provided to the researcher in a coded manner by a trusted individual outside the study. Patients were

followed up for one month and underwent clinical examinations once a week.

Additionally, telephone calls were made every three days to check on the severity of pain. Information on each patient, such as age, gender, body mass index (BMI), and smoking status, was recorded. Relevant clinical information, including radiation dose, primary tumor location, and tumor histology, was extracted from the patients' medical records.

Cancer staging was determined in consultation with an oncologist using the TNM (Tumor, Nodes and Metastasis) classification of malignant tumors. The initial diagnosis of OM study inclusion was made in collaboration with an oncologist and an oral and maxillofacial specialist. OM grading was assessed according to the guidelines set out by the WHO (Table1)(Glick 2015).

Table 1. Grading of OM

Grade	Definition
0	None
1	Pain and redness
2	Redness, ulceration, ability to eat solid foods
3	Ulceration, need for liquid diet
4	Feeding impossible

Pain intensity was evaluated by asking the patient questions and using the Visual Analogue Scale (VAS). One examiner (F. SH) conducted all clinical procedures and examinations. F,SH was calibrated for intra- and inter examiner measurement error, which involved measuring OM grading and pain intensity on multiple occasions, both by her and by an oral medicine and maxillofacial specialist.

Statistical analysis

T-test, and Chi-square test were employed to compare baselines measurements. To analyze the changes in OM grade and pain severity between the two groups, a repeated measures ANOVA was conducted, controlling for confounding factors. All data analyses were conducted using IBM SPSS Statistics version22 (IBM Corp., Armnok, NY, USA). Values are expressed as mean ± standard deviation. Statistical significance was set at $p<0.05$.

Outcomes

The primary outcome was the change in pain intensity, measured every three day using the VAS.

The secondary outcome was the change in OM grade, assessed weekly based on WHO oral mucositis criteria.

Tooth color changes were monitored as an exploratory outcome, assessed before and after the intervention using the Vita Shade Guide in patients with remaining teeth.

Results

This study involved 68 patients undergoing radiation therapy, with 34 patients receiving saffron for the treatment of OM (saffron spray group), and the other 34 receiving Mucosamin® spray (Mucosamin® spray group). Among the participants, 28 patients (82.4%) in the saffron group and 27 patients (79.4%) in the Mucosamin® group were male. However, there was no statistically significant difference in gender distribution between the two groups (p=0.75). Additionally, the two groups did not show any significant differences in age, body mass index (BMI), or radiation dosage (Table 2).

Table 2. Comparison of age, BMI, and radiation dose between the two groups (t-test and chi-square)

Variable	Group	Mean±SD	p-value
BMI (kg/m^2)	Saffron	23.3±0.99	0.21
	Mucosamin®	23±1.05	
Age (years)	Saffron	53.8±8.04	0.93
	Mucosamin®	54±6.73	
Radiation dose (Gy)	Saffron	60.4±6.67	0.36
	Mucosamin®	61.9±6.51	

Most patients in both groups had a positive smoking history, with 24 individuals (70.6%) from both the saffron and Mucosamin® groups being smokers. Again, there was no statistically significant difference between the groups concerning smoking status (p=1.00).

Many patients in both groups did not report any history of underlying disease (29 patients in the saffron group and 26 in the Mucosamin® group). Upon further analysis, the most common underlying condition noted was increased blood lipids, found in two patients from the saffron group. Additionally, three patients in the Mucosamin® group had both hypothyroidism and increased blood lipids. Also, most of the patients did not report any history of medication use. However, the most frequently mentioned medication was atorvastatin, reported by two patients in the saffron group and three patients in the Mucosamin® group.

As shown in Table 3, the majority of the patients with HNCs were classified stage 1, while stage 3 had the fewest cases. There was a statistically significant difference in cancer stage between the two groups (p=0.01), with the majority of patients in the saffron consumption group being diagnosed at stage 1. This statistical difference was confirmed through further analysis.

In terms of histological findings, both groups showed similar results. The frequency of squamous cell carcinoma (SCC) was 30 patients (88.2%), while mucoepidermoid carcinoma accounted for 4 patients (11.8%). There was no statistically significant difference in histological types between the two groups (p=1.00).

An examination of the primary tumor sites (Table 4) revealed that the highest frequency of cases was associated with the larynx and nasopharynx. Both groups showed the same frequency, with 8 patients (23.5%) having laryngeal tumors and 6 patients (17.6%) having nasopharyngeal tumors.

Most patients in both groups were toothless at the beginning and end of the study. At the start, 25 (73.5%) in the saffron group and 26 (76.5%) patients in the Mucosamin® group were edentulous. For those who had teeth, tooth color was assessed using the Vita Shade Guide in a controlled environment with consistent lighting, both before and after the intervention.

Table 3. Comparison of stage of HNCs between the two groups

			Stage			**p-value**
			1.00	**2.00**	**3.00**	
Groups	Saffron	Number	28	3	3	0.01
		Percentage	82.4%	8.8%	8.8%	
	Mucosamin®	Number	19	13	2	
		Percentage	55.9%	38.2%	5.9%	

Table 4 -.Primary tumor site in the two groups

Group		**Primary tumor site**									
		Tongue	**Parotid gland**	**Submandibular gland**	**Larynx**	**Hodgkin's**	**Buccal mucosa**	**Upper esophagus**	**Mandible**	**Nasal cavity**	**Nasopharynx**
1	Number	0	2	4	8	0	4	5	5	0	6
	Percentage	0%	5.9%	11.8%	23.5%	0.0%	11.8%	14.7%	14.7%	0.0%	17.6%
2	Number	3	2	2	8	2	0	4	6	1	6
	Percentage	8.8%	5.9%	5.9%	23.5%	5.9%	0.0%	11.8%	17.6%	2.9%	17.6%

As shown in Table 5 and Figure 2, pain intensity decreased from the start of the study to the fourth week in both groups. At the beginning of the study, pain intensity was recorded as 6.29 ± 1.61 for the saffron group and 6.70 ± 1.93 for the Mucosamin® group. By the fourth week, these values decreased to 3.61 ± 1.35 and 4.00 ± 1.23, respectively. However, there was no statistically significant difference in pain intensity between the two groups (p=0.38). This indicates that brewed saffron spray is as effective as Mucosamin® spray in reducing pain intensity.

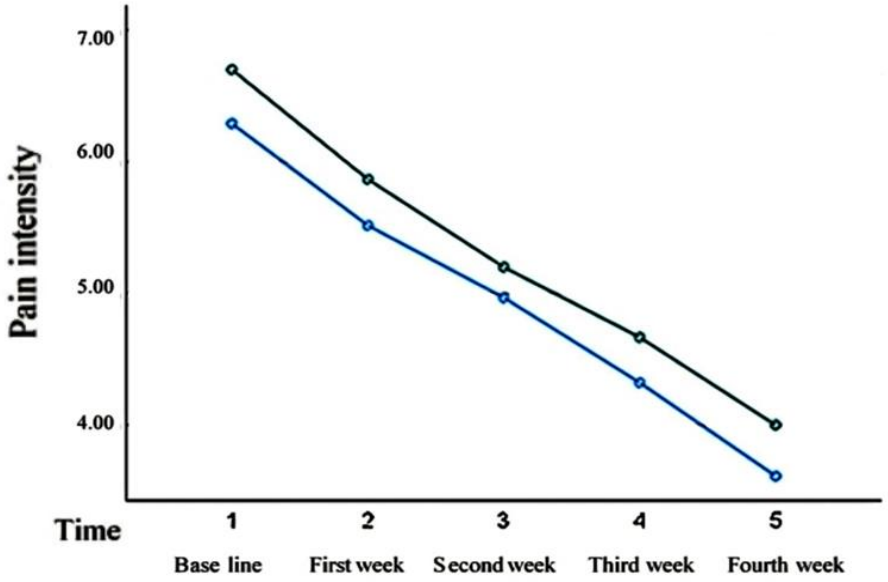

Figure2. Comparison of pain intensity in the two groups(blue color: saffron and green color: *Mucosamin®)*

Table 5. Comparison of pain intensity in two groups

Pain intensity	Group	Number	Mean (95%CI)	p- value between groups*
Baseline	Saffron extract	31	6.29(5.71,6.86)	0.38
	Mucosamin®	30	6.70(6, 7.39)	
End of first week	Saffron extract	31	5.51(4.83,6.18)	
	Mucosamin®	30	5.86(5.17,6.54)	
End of second week	Saffron extract	31	4.96(4.35,5.56)	
	Mucosamin®	30	5.20(4.58,5.81)	
End of third week	Saffron extract	31	4.32(3.75,4.88)	
	Mucosamin®	30	4.66(4.13,5.18)	
End of fourth week	Saffron extract	31	3.61(3.12,4.09)	
	Mucosamin®	30	4.00(3.55,4.44)	

* Analyzed with repeated measures ANOVA Adjusted for cancer stage

Table 6 and Figure 3 show that the average OM grade at the end of the study (fourth week) was significantly lower in both groups compared to the beginning of the study. At the outset, the average OM grade was 2.87 ± 0.34 for the saffron group and 2.56 ± 0.50 for the Mucosamin® group.

By the end of the study, these grades decreased to 2.70 ± 0.46 and 2.40 ± 0.49, respectively. Nevertheless, there was no significant difference between the two groups in terms of the reduction in OM grading, indicating that both treatments were equally effective (p=0.246).

Importantly, none of the participants reported any side effects related to the use of the intervention medications.

Table 6- Comparison of OM grade in the two groups

OM grade	Group	Number	Mean (95%CI)	p- value between groups*
Baseline	Saffron extract	31	2.87(2.74,2.99)	0.246
	Mucosamin®	30	2.56(2.38,2.73)	
End of first week	Saffron extract	31	2.80 (2.65,2.94)	
	Mucosamin®	30	2.43(2.25, 2.60)	
End of second week	Saffron extract	31	2.70(2.53,2.86)	
	Mucosamin®	30	2.43(2.25,2.60)	
End of third week	Saffron extract	31	2.67(2.50,2.83)	
	Mucosamin®	30	2.40(2.22,2.57)	
End of fourth week	Saffron extract	31	2.70(2.53,2.86)	
	Mucosamin®	30	2.40(2.22,2.57)	

* Analyzed with repeated measures ANOVA Adjusted for cancer stage

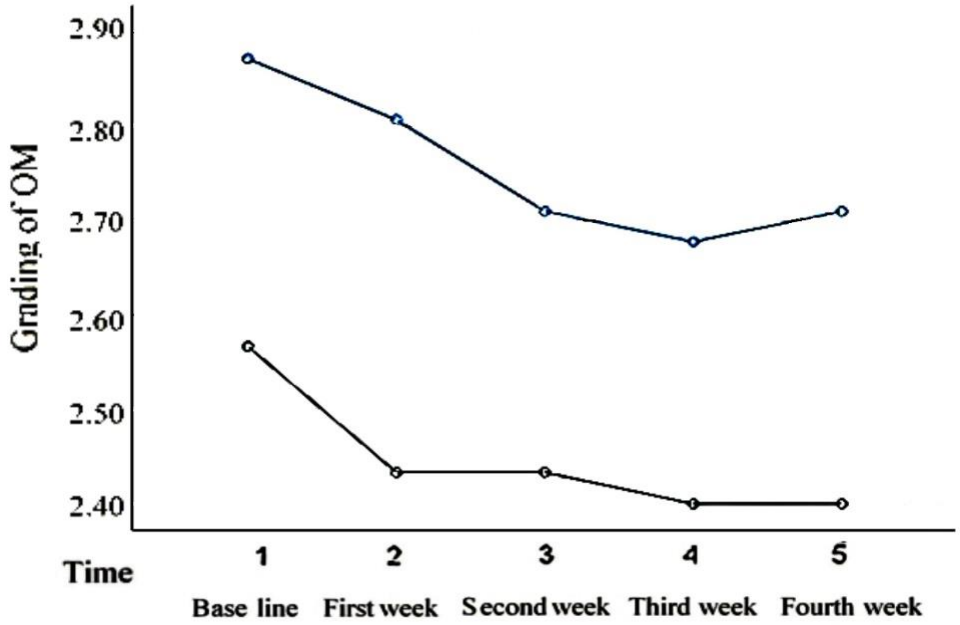

Figure3. Comparison of grading of OM in the two groups(blue color: saffron and green color: *Mucosamin®)*

Discussion

The use of herbal medicines in disease treatment has garnered significant interest within the scientific medical community.

Saffron, a medicinal plant from the Iridaceae family, possesses various therapeutic properties (Anaeigoudari, Anaeigoudari and Kheirkhah-Vakilabad 2023). The primary bioactive compounds in this traditional plant are crocin ($C_{44}H_{64}O_{24}$), safranal ($C_{10}H_{14}O$), and picrocrocin ($C_{16}H_{26}O_7$), which contribute to saffron's color, aroma, and flavor, respectively (Zeinali et al. 2019). The antioxidant and anti-inflammatory effects of saffron are predominantly attributed to crocin, found in the saffron stigma (Cerdá-Bernad et al. 2022). Its anti-inflammatory properties inhibit the activity and transfer of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) to the nucleus, thereby reducing the transcription of inflammatory factors such as Tumor Necrosis Factor Alpha (TNF-α)(Azgomi et al. 2022).

This study was designed as a randomized controlled clinical trial to compare the efficacy of brewed saffron spray against Mucosamin® in relieving radiotherapy-induced OM. The results suggest that saffron can be an effective

adjunctive treatment alongside existing medications for alleviating pain and reducing the severity of OM.

Most clinical trials involving saffron have utilized saffron capsules, and those that examined saffron extract or juice did not assess tooth color. Consequently, no research exists to confirm or refute findings related to tooth discoloration in this study. Nonetheless, the absence of tooth discoloration observed may be attributed to the short duration of consumption and the low concentrations of saffron used.

Analysis of mean pain intensity from the study's outset to its conclusion indicated a significant reduction in mean pain intensity by week 4 compared to baseline. However, no statistically significant difference was observed between the two groups regarding pain intensity or OM grading. Considering that pain from OM severely compromises a patient's quality of life, and high-grade OM often leads to inadequate food intake, many patients may become severely malnourished and require parenteral nutrition. Moreover, research indicates that approximately 15% of patients experience early radiotherapy termination or dose adjustments, emphasizing that OM-related pain can impact survival. Therefore, managing mucositis-related pain is crucial for the clinical management of cancer patients.

Currently, supportive care is the main recommended treatment approach, with analgesics being the most frequently prescribed medications for pain control in OM. Morphine is endorsed by the MASCC/ISOO guidelines for pain associated with OM resulting from chemotherapy and radiotherapy in patients undergoing hematopoietic stem cell transplantation (Lalla et al. 2014). Additionally, mouthwashes or rinses containing morphine are often prescribed for HNC patients experiencing high-grade OM. Various "magic" mouthwashes have also been formulated to alleviate pain, typically containing anesthetics, antacids, diphenhydramine, and occasionally steroids. However, none of these treatments are without side effects and lack universal approval (Blakaj et al. 2019).

In a study conducted by Forouzanfar et al., the anti-inflammatory effects of saffron on gingival indices were investigated in patients with generalized marginal plaque-induced gingivitis. The results indicated a statistically significant relationship between gingival indices measured before and one month after the use of saffron toothpaste. Notably, in the saffron-treated group, there was a significant reduction in both gingival indices (GI) and bleeding on probing (BOP) compared to the placebo group. However, no statistically significant differences were observed regarding pocket depth (PD) and plaque indices (PI). Overall, the study demonstrated that the incorporation of aqueous saffron extract in toothpaste positively affected certain gingival indices in patients suffering from gingivitis (Forouzanfar et al. 2016). In another investigation by Meybodi et al., the anti-inflammatory effects of saffron were assessed in patients with moderate to severe generalized periodontitis. The findings showed a significant difference in gingival indices when comparing measurements taken before and four weeks after employing both chlorhexidine and saffron mouthwashes. However, no statistically significant difference was found between the two treatment groups, suggesting that the effectiveness of the saffron mouthwash was comparable to that of the chlorhexidine mouthwash. Additionally, patients reported a higher satisfaction with the taste of the saffron mouthwash compared to the chlorhexidine option (Maybodi et al. 2022). Khalatbari-Mohseni et al. studied the effects of crocin, a component of saffron, on psychological parameters of patients undergoing methadone maintenance treatment (MMT). In this study, 50 patients were randomly assigned to receive either 30 mg of crocin or a placebo daily for eight weeks, 1-hour post-meal. Psychological assessments were conducted at the beginning and end of the

trial. The findings indicated that crocin positively influenced the mental health status of patients undergoing MMT, suggesting it may be recommended as an adjunctive supplement in opioid withdrawal protocols due to its potential to enhance quality of life and mitigate opioid-related side effects (Khalatbari-Mohseni et al. 2019). The findings from these studies collectively support the analgesic and anti-inflammatory properties of saffron, which could lead to a reduction in pain intensity in the saffron-treated groups, especially for conditions like radiotherapy-induced OM in HNC patients.

Furthermore, the study examined the severity of OM, revealing that the average grade of OM decreased by the fourth week, indicating a statistically significant difference between the two groups. The development of OM is influenced by numerous variables including the anticancer treatment regimen, dosage, number of cycles, and patient characteristics. Notably, female patients, those of older age, with higher body weight, reduced drug clearance, and certain genetic predispositions are at an increased risk of severe OM, particularly when treated with 5-Fluorouracil (5-FU) (Chansky, Benedetti and Macdonald 2005; Pulito et al. 2020). Interestingly, patients with conditions characterized by aberrant epithelial cell proliferation such as psoriasis, exhibit a reduced incidence of OM. In general, female gender, older age, high body weight, reduced drug clearance, and genetic predisposition are recognized as risk factors for the development of OM. Precise epidemiological data on the frequency of OM is lacking, as this condition is often documented only when patients develop severe OM and require clinical treatment (Pulito et al. 2020).

Additionally, there is currently no standard scale for grading the severity of OM, making it challenging to compare the grading and assessment of the disease. Different scales are employed to determine the degree of OM, each considering various parameters. For instance, the WHO scale for assessing OM evaluates objective criteria including the presence of erythema or ulceration, which reflect the patient's ability to eat. The Oral Mucositis Assessment Scale (OMAS) utilizes a quantitative scale that measures the size of the ulcer. The Eastern Cooperative Oncology Group (ECOG) Mucositis Scale is also referenced in the Common Toxicity Criteria Guidelines, categorizing mucositis severity based on the anatomical site of occurrence. Similarly, the National Cancer Institute (NCI) provides a mucositis severity scale in its Common Terminology Criteria for Adverse Events (CTCAE), which is based on both the anatomical site of development and the type of treatment, whether chemotherapy or radiotherapy (Lalla, Sonis and Peterson 2008).

In another study, Barani-Karbaski et al. examined the antimicrobial effects of aqueous and alcoholic extracts of saffron on pathogenic oral microbes. Their research found that both extracts exhibited inhibitory effects on three microbes: *Streptococcus mutans*, *Lactobacillus*, and *Candida albicans*. However, the effectiveness of saffron extracts was lower compared to standard antibiotics, like penicillin, and there was a statistically significant difference in antibacterial effects between saffron extracts and penicillin on all three microbes. Furthermore, the study indicated that the alcoholic extract of saffron was more effective than the aqueous extract in eliminating *Candida albicans* and *Streptococcus mutans* (Barani Karbasaki et al. 2016) . As the secretion and subsequent rinsing of saliva decrease in patients with OM, the number of pathogenic microbes in their mouths tends to increase, making them more susceptible to various bacterial and fungal infections. Therefore, using saffron is recommended to reduce the number of harmful microbes in the mouth, such as *S. mutans* and *C. albicans*, thereby lowering the risk of bacterial and fungal infections.

Our study had several limitations, including a small sample size and a short

duration for both the study and patient follow-up. Therefore, we recommend that future studies involve larger sample sizes and longer follow-up periods. Additionally, it is important that future research controls for all factors that could affect the results, particularly the stage of cancer in the two groups, ensuring there are no statistically significant differences between them.

Moreover, examining biomarkers of inflammation and oxidative stress in the blood or saliva of participants could provide valuable insights. From the perspective of traditional medicine, it would also be beneficial to include the temperament factor of participants in the research design of future studies.

In conclusion, our study found that brewed saffron spray was as effective as Mucosamin® in reducing pain intensity and grading of OM in patients with radiotherapy-induced OM. However, we recommend that further studies investigate the precise effects of saffron at various doses on this condition.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Ethical Considerations

IRCT registration number: IRCT20221207056743N1

Code of Ethics

Ethics code IR.MUQ.REC.1401.229 in Qom University of Medical Sciences, Iran.

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