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# Efficacy of the *plantago major* L. syrup on radiation induced oral mucositis in head and neck cancer patients: A randomized, double blind, placebo-controlled clinical trial

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ABSTRACT

*Introduction:* Oral mucositis is a complication of radiation therapy in cancer patients. We designed a trial to evaluate efficacy of plantago major on symptoms of radiation induced mucositis in cancer patients.
*Methods:* In this randomized double blind, placebo-controlled trial 23 patients received plantago major syrup as intervention group and 23 patients received placebo syrup as control group for 7 weeks. Outcome measures were severity of mucositis according to WHO scale and severity of patients' pain assessed by visual analogue scale.
*Results:* Severity of mucositis were significantly lower in intervention group compared to placebo group (p value $< 0.05$). Also patients in intervention group experienced significantly less pain compared to placebo group during radiotherapy period (p value $< 0.05$)
*Conclusion: Plantago major* L syrup was effective on the reduction of the symptoms of radiation induced mucositis in patients with head and neck cancers.

## 1. Introduction

Head and neck cancers are the most common malignancy in the world. These two types of cancer account for about 4% of all types of malignancies. Radiotherapy and chemotherapy are the most widely used interventions for the treatment of these cancers.[1] Oral mucositis, as a major non-hematologic complication of radiation and chemotherapy treatments, result in the patients' morbidity and mortality.[2–4] This complication is associated with significant morbidity, odynodysphagia, pain, dysgeusia, and the subsequent dehydration and malnutrition.[5,6]It may considerably affect cancer treatment and the patient's quality of life.[7,8]

Currently, there is no absolutely effective treatment for preventing mucositis.[9]Despite the availability of many remedial agents that claim to prevent or treat oral mucositis often takes a treatment refractory turn, necessitating the researches to find new options.نامفهوم.

*Plantago major* L is an old medicinal plant used in Persian medicine as an effective wound healing agent.[10]Particularly, in the main traditional Persian medicine texts such as the Canon of Medicine by Avicenna (980–1037 AD),[11] Rhazes' Liber Continens (854–925 AD), [12] and the Storehouse of Medicaments by *Aghili Shirazi* (1670–1747 CE),[13] it was prescribed for a wide variety of gastrointestinal and dermatologic complaints. [14,15] A range of biological activities has been found from *plantago major* L, including anti-inflammatory, analgesic, wound healing and antiulcerogenic activity, antioxidant, antimicrobial and immuno modulating activity.[16] Therefore, it could be an effective choice in treatment of mucusitis. Therefore, we designed a randomized controlled clinical trial to evaluate the efficacy of *plantago major* L on reduction of the symptoms of radiation-induced mucositis in patients with head and neck cancers.

## 2. Material and methods

### 2.1. Trial design

This study was designed as a prospective double arm, randomized,

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double blind, and placebo-controlled clinical trial. In this trial, we evaluated the efficacy of oral consumption of *plantago major* L syrup on reduction of symptoms of radiation-induced mucositis in the head and neck cancer patients. No changes occurred to methods after trial commencement.

### 2.2. Compliance with ethical issues

The study basis was in compliance with the guidelines of Declaration of Helsinki (1989 revision) Declaration. Local Medical Ethics Committee of Arak University of Medical Sciences approved this trial as well (Approval number: IR.ARAKMU.REC.1397.059). A signed written informed consent form received from all participants. Moreover, the study was registered by Iranian Registry of Clinical Trials with the code: IRCT20190312043027N1.

### 2.3. Participants

The inclusion criteria for participants enrolled in this study were men and women aged 18–65 years who had head and neck cancer and were candidate to receive radiotherapy. Life expectancy of more than one year based on the estimates of the physician or medical team, physical and mental ability to cooperate in filling out the questionnaire, willingness to participate in the study, and absence of neutropenia and immune system suppression were the other inclusion criteria of this study. Exclusion criteria were consumption of alcohol, antidepressants, opioids, antihypertensives, antihistamins, diuretics, mouthwashes, and artificial saliva. History of previous head and neck radiation therapy or chemotherapy in the past six months; history of connective tissue diseases such as sjogren, rheumatoid arthritis, systemic lupus erythematous, liver and kidney disease; major depression; and diabetes mellitus were the other exclusion criteria of this study. Patients with mucositis grades 3 and 4 or oral candidiasis and herpes, or patients requiring hospitalization during radiotherapy were also excluded.

### 2.4. Intervention

After obtaining informed consent from the enrolled patients, the researcher randomly assigned them to receive *plantago major* L syrup as the intervention group or placebo syrup as the control group. Patients in intervention group were instructed to take the drug three times daily from three days before the start of radiotherapy to the end of it. Patients were advised not to rinse their mouth for half an hour after taking the drug. They received *plantago major* L syrup (were prepared according to USP 34 simple syrup method in medicinal plants Lab, School of Pharmacy, Shahid Behesti University of Medical Sciences, Tehran, Iran) 7.5 cc, three times a day for 7 weeks. Patients in the placebo group received placebo syrup (simple sugar syrup of 66.7% prepared based on United States Pharmacopeia) 7.5 cc, three times a day for 7 weeks. All patients in both group were treated with radiotherapy at a dose of 2 Gy per day for 5 days per week, and the minimum therapeutic dose for the patients was 50 Gary. The radiotherapy device used was a Siemens Primus X-ray linear accelerator (2012) with 6 and 15 MV photon energies.

All patients were advised to follow the standard protocol of health care[17]: clean the mouth with a toothbrush and baby toothpaste two to three times a day; rinse the mouth with sufficient water after each meal; avoid hot, spicy and sour foods; avoid smoking and alcohol; and rinse the mouth with normal saline 4–6 times per day.

### 2.5. Randomization and blinding

Forty six eligible participants were randomized in two parallel groups. Convenience sampling method was used for all participants with head and neck cancer. They were candidates to receive radiotherapy and referred to Isfahan Omid Hospital and Kashan Yasrebi Hospital in Iran. The participants were divided into two groups via blocked randomization method. To assign a target group to one of the two groups, the block randomization list was generated by astatistician using Random Allocation Software with a block size of 4. All the participants and investigators were blind to the allocation of the patients. Because the placebo syrup bottle was similar to *plantago major* L syrup in the same color, shape and weight, the physician and patient were blinded to the type of intervention.

### 2.6. Outcomes

Primary outcome measure of this clinical trial was the severity of oral mucositis assessed by the investigator according to WHO scale in every visit. Secondary outcome measures included severity of the patients' pain by visual analogue scale (VAS). In addition, the side effect of the intervention was the other secondary outcome measure.

### 2.7. Statistical analysis

According to the previous study and the preventive effects of the drug, with an effect size of 0.5, type I error of 0.05, power of 80%, and dropout rate of 10%, the sample size was calculated 23 individuals in each group by using GPower software version 3.[18]

Data were presented as the mean and standard deviation (SD). Baseline variables were compared between the two groups by independent sample *t*-test and chi-square test. Repeated measures analysis and independent sample *t*-test was used to compare the efficacy of the intervention between the two groups. The Statistical Package for Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The significance level was set at $< 0.05$.

## 3. Results

### 3.1. Study flow and baseline characteristics of the patients

From October 2018 to July 2019, sixty patients were evaluated for eligibility. Of this number, 46 had the inclusion criteria and signed the consent form to participate in the trial. Twenty three patients were assigned to the intervention group and 23 to the placebo group. Fig. 1 is a flow diagram of the groups' enrollment, allocation, intervention, follow up, and analysis.

Baseline demographic data and clinical features of the study patients are shown in Table 1. None of the baseline characteristics of the participants showed significant differences between the two study groups ($p > 0.05$).

### 3.2. Clinical response

As shown in Fig. 2, the result of comparison between the two groups showed that severity of oral mucositis was significantly lower in the intervention group compared to the placebo group from the start of radiotherapy to the seventh week of treatment(p value $< 0.05$).

Descriptive statistics of mucositis severity in the studied groups are shown in Table 2.

Similar results were observed for the patients' pain, so that patients in the intervention group experienced significantly less pain compared to the placebo group during the radiotherapy period (p value $< 0.05$) (Fig. 3).

Descriptive statistics of pain severity in the studied groups are shown in Table 3.

### 3.3. Safety and tolerability

One patient in the placebo group developed tolerable headache. In the intervention group, one patient had transient nausea and one suffered mild abdominal cramp, but all of them continued their

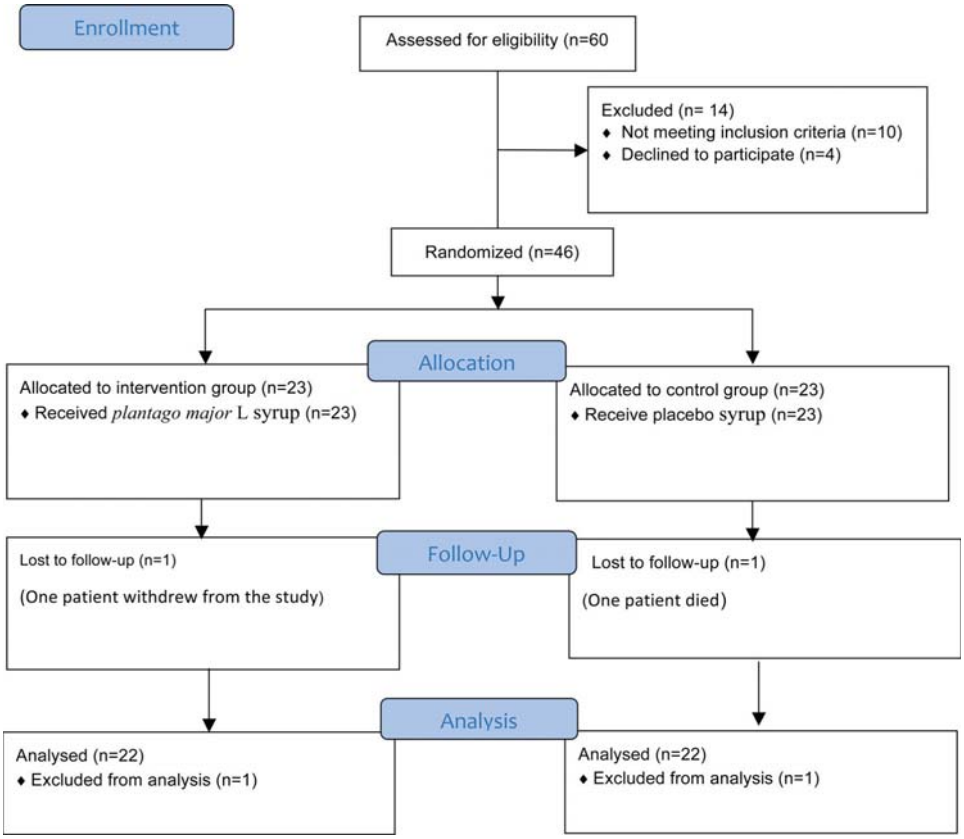


**Fig. 1.** Flow diagram of the enrolment, groups' allocation, interventions, follow up, and final analysis.

**Table 1**
Baseline demographic data and clinical features of the both study groups.

| Baseline Characteristics | *Plantago major L* group (n = 22) | Placebo group (n = 22) | P- value |
|---|---|---|---|
| **Age** (Year), Mean ( ± SD) | 54.09(14.41) | 58.86(17.29) | 0.326 |
| **Body mass index** ($kg/m^2$),Mean( ± SD) | 25.58(3.23) | 34.82(42.01) | 0.363 |
| **Sex (**Male/Female) N | 16/6 | 14/8 | 0.517 |
| **Smoker**(Yes/No) | 5/17 | 7/15 | 0.498 |
| **White blood cell**($\times 10^3\mu l$) | 5.34(1.97) | 5.58(1.88) | 0.684 |
| **Radiation dose**(Gray) | 6272.72(293.06) | 6372.72(356.14) | 0.315 |
| **Primary** tumour **site(n)** | | | 0.938 |
| Maxillary sinus | | 2 | |
| Floor of mouth | 1 | 2 | |
| Nasopharynx | 1 | 8 | |
| Salivary glands | 11 | 3 | |
| Buccal mucosa | 2 | 1 | |
| Tonsil | 2 | 1 | |
| Tongue | 1 | 5 | |
| | 4 | | |
| **Tumor stage(n)** | | | |
| Stage 2 | 13 | 12 | 0829 |
| Stage 3 | 8 | 9 | |
| Stage 4a | 1 | 2 | |

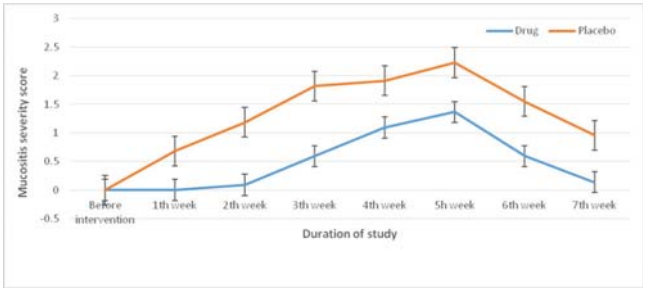


**Fig. 2.** The trend of mucositis severity change was evaluated by WHO scale during the study period.

intervention.

## 4. Discussion

Mucositis is a disturbing complication of anticancer therapy that affects 40–80% of cancer patients receiving chemotherapy and approximately half of those undergoing radiotherapy of the head and neck.[19,20]Questions about the safety of synthetic agents that are used to heal the mucositis, and interactions of these agents with other drugs have caused the researchers to consider herbal remedies for the reduction of symptoms of mucositis. Ravleen Nagi et al. compiled evidence-based studies on the effectiveness of natural agents in the management of oral mucositis induced by chemotherapy or radiotherapy in cancer patients in 2018.[19] They performed computerized literature searches and identified twenty six randomized controlled trials. Most studies showed a statistically significant result, demonstrating the efficacy of natural agents with minimal side effects. Herbs such as *Isatis indigotica Fort*, *Achillea Millefolium, Calendula officinalis,* and *Matricaria chamomilla* L. were reported to have positive preventive and therapeutic effects on mucositis. [21–24]

In the present study, we evaluated the efficacy of *plantago major* L syrup in the prevention of radiation induced mucositis in patients with head and neck cancers via a double blind randomized placebo-controlled clinical trial. The *plantago major L* syrup was effective in reduction of the radiation-induced mucositis severity.

To the best of our knowledge, this is the first clinical trial that examined the effectiveness of the *plantago major L* in patients with radiation-induced mucositis. A previous study evaluated the efficacy of plantago major extract versus sodium bicarbonate 5% versus

**Table 2**
Descriptive statistics of mucositis severity evaluated by WHO scale in the studied groups.

| Outcome (Mucositis severity) | Drug group (n = 22) Mean (SE) | Placebo group (n = 22) Mean (SE) | P value* | Mean Difference(%95 Confidence Interval) |
|---|---|---|---|---|
| 1th week | 0.00 ± 0.00 | 0.68 ± 0.10 | < 0.001 | −0.68 (-0.89 to -0.47) |
| 2 th week | 0.09 ± 0.06 | 1.18 ± 0.10 | < 0.001 | −1.09 (-1.34 to -0.83) |
| 3 th week | 0.59 ± 0.10 | 1.82 ± 0.08 | < 0.001 | −1.22 (-1.50 to -0.95) |
| 4 th week | 1.09 ± 0.06 | 1.91 ± 0.06 | < 0.001 | −0.81(-0.99 to -0.63) |
| 5 th week | 1.36 ± 0.10 | 2.23 ± 0.09 | < 0.001 | −0.86 (-1.14 to -0.58) |
| 6 th week | 0.59 ± 0.10 | 1.55 ± 0.10 | < 0.001 | −0.95 (-1.26 to -0.64) |
| 7 th week | 0.14 ± 0.07 | 0.95 ± 0.08 | < 0.001 | −0.81 (-1.03 to -0.59) |
| P value** | < 0.001 | < 0.001 | | |

* P-value from Independent-Sample *t*-test.
** P-value from ANOVA (Repeated Measure).

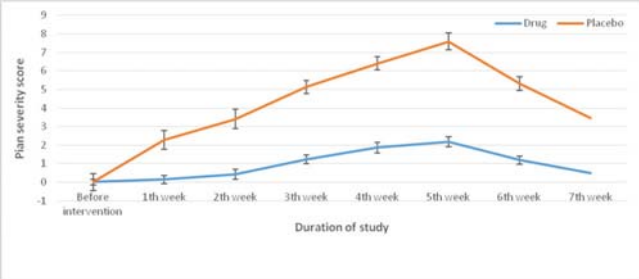


**Fig. 3.** The trend of visual analogue scale (VAS) change of pain during the study period.

chlorhexidine 0.12% in the symptomatic treatment of chemotherapy-induced oral mucositis in solid tumour cancer patients.[18] Cabrera-Jaime et al. in this study did not find this treatment to be more beneficial than sodium bicarbonate or chlorhexidine. There are differences between our study and Cabrera-Jaime et al.'s study. First, the patients in our study had radiotherapy-induced mucositis, whereas those in their study had chemotherapy-induced mucositis. Secondly, we compared *plantago major* L syrup versus placebo, while they evaluated the efficacy of *plantago major* extract versus sodium bicarbonate 5% versus chlorhexidine 0.12%. Thirdly, our study time was longer (7 weeks vs. 2 weeks). These differences may result in different findings of these two studies.

The main biochemical components of *plantago major* L are ursolic acid, oleanolic acid and α-linolenic acid, and anti-inflammatory and anti-tumor effects of this plant could be attributed to these components.[14]These major compounds have shown to exert inhibitory effects on COX-2 catalyzed prostaglandin production. Also, luteolin-7-O–glucoside, as the major flavonoid present in this plant, inhibits a series of human cancer cell lines via acting as a potent DNA topoiso-merase I poisons.[25]It inhibits leukemic cell proliferation and induces apoptosis by inhibition of the RSK1 pathways, too. Moreover, the luteolin has the ability to suppress the leukocyte migration which could be considered as anti-inflammatory effect.[26]

### *4.1. Study limitations*

The small sample size was one of the limitations of this study. However, the minimum sample size may be acceptable for this sre-search as a pilot study in cancer patients. Of course, regarding the positive results of this study, it is recommended that further studies should be conducted with a larger sample size. Although we used WHO scale for assessment of the patients' mucositis severity as a valid and reliable tool, another limitation was lack of an objective tool for assessment of the patients' mucositis. Of course, the use of more precise evaluation tools, such as biopsy, has also ethical considerations. Another limitation was the lack of more baseline characteristic factors such as stage of cancer, extent of the irradiated field, oral hygiene state, dental prosthesis usage, and salivary floe rates. It is recommended that future studies should include these baseline factors.

## 5. Conclusion

According to the results of this clinical trial, we concluded that oral use of *plantago major* L syrup was effective on reduction of the symptoms of radiation-induced mucositis in patients with head and neck cancers.

## CRediT authorship contribution statement

**Gholamreza Mohammad Soltani:** Conceptualization, Methodology, Software. **Simin Hemati:** Writing - review & editing. **Mostafa Sarvizadeh:** Visualization, Investigation. **Mohammad Kamalinejad:** Software, Validation. **Vahid Tafazoli:** Data curation, Writing - original draft. **Seied AmirHossein Latifi:** Supervision.

## Declaration of Competing Interest

None.

**Table 3**
Descriptive statistics of pain severity evaluated by VAS in the studied groups.

| Outcome (pain severity) | Drug group (n = 22) Mean (SE) | Placebo group (n = 22) Mean (SE) | P value* | Mean Difference (%95 Confidence Interval) |
|---|---|---|---|---|
| 1th week | 0.14 ± 0.07 | 2.14 ± 0.22 | < 0.001 | −2.00 (-2.48 to -1.52) |
| 2 th week | 0.41 ± 0.10 | 3.00 ± 0.24 | < 0.001 | −2.59 (-3.14 to -2.04) |
| 3 th week | 1.23 ± 0.13 | 3.91 ± 0.24 | < 0.001 | −2.68 (-3.24 to -2.11) |
| 4 th week | 1.86 ± 0.11 | 4.55 ± 0.17 | < 0.001 | −2.68 (-3.10 to -2.26) |
| 5 th week | 2.18 ± 0.14 | 5.41 ± 0.17 | < 0.001 | −3.22 (-3.67 to -2.78) |
| 6 th week | 1.18 ± 0.12 | 4.14 ± 0.22 | < 0.001 | −2.95 (-3.47 to -2.43) |
| 7 th week | 0.50 ± 0.10 | 2.95 ± 0.18 | < 0.001 | −2.45 (-2.88 to -2.02) |
| P value** | < 0.001 | < 0.001 | | |

* P-value from Independent-Sample *t*-test.
** P-value from ANOVA (Repeated Measure).

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