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# Evaluating Ayurvedic mouthwash and soda-salt mouthwash for oral mucositis in head and neck cancer: A randomized controlled trial

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ABSTRACT

*Background:* Patients undergoing radiotherapy (RT) or concurrent chemo-radiation (CCRT) for head and neck squamous cell carcinoma (HNSCC) often suffer from side effects such as mucositis, xerostomia, pharyngitis, laryngitis, and pain, which are being managed symptomatically by alcohol-based mouthwashes.
*Objectives:* To determine the effectiveness of Ayurvedic mouthwash "*Draksha Guduchyadi Kashaya*" in reducing the severity of oral side effects of chemo-radiation.
*Material and methods:* This concurrent parallel randomized controlled study was conducted at Sir Sunderlal Hospital, BHU, on 70 HNSCC patients scheduled to undergo RT/CCRT. Patients who met the inclusion-exclusion criteria were enrolled, and 35 were randomly assigned to either the intervention group (Ayurveda) or the control group using a simple random technique (lottery method). Blinding was not implemented in this study. Patients in the intervention group (Ayurveda) were instructed to perform *kavala* with 50 ml of "*Draksha Guduchyadi Kashaya*" for 2 min, ten times daily, while the control group performed 2-min gargling with soda-salt mouthwash ten times daily.
*Results:* Out of the 70 patients enrolled, data from 60 patients were analyzed, revealing statistically significant differences in the onset of mucositis ($p = 0.049$), pharyngitis ($p = 0.034$), laryngitis ($p = 0.009$) and intensity of variables such as mucositis ($p = 0.000$), xerostomia ($p = 0.046$), pharyngitis ($p = 0.002$), laryngitis ($p = 0.035$), and pain ($p = 0.000$). These findings indicate that Ayurvedic mouthwash may be beneficial in managing the oral side effects of chemo-radiation in HNSCC.
*Conclusion:* This AYUSH financially supported trial (Reg No: CTRI/2020/04/024672) demonstrates promise as a safe and cost-effective alternative for managing oral complications of RT/CCRT, offering complementary treatment for comprehensive cancer care.

## 1. Introduction

### 1.1. Back ground and rationale

Cancer, *The Emperor of All Maladies*, has become a metaphor for death in the modern societies [1]. As per the latest data by WHO, cancer is the first leading cause of death before the age of 70 in more than 112 countries [2]. Further, among various melanomas, head and neck squamous cell carcinoma (HNSCC) ranks as the sixth most common cancer in the world [3]. HNSCC is estimated to contribute to more than 8,90,000 new cancer cases and more than 4,50,000 deaths annually [4]. India is not different from other parts of the world regarding cancer prevalence.

The primary treatment for HNSCC is surgical resection, followed by either chemotherapy, radiotherapy, or chemo-radiation, depending on the stage of the disease. However, studies suggest that these treatments

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may sometimes lead to specific side effects that can deteriorate the quality of life (QOL). Mucositis, xerostomia, dental caries, candidiasis, dysgeusia, osteoradionecrosis, soft tissue necrosis, trismus, and progressive periodontal attachment loss are some of the after-effects of radiotherapy, capable of making a significant impact on a patient's QOL [5].

Since the entire motive of the medical team during the treatment regime is to defeat the dangerous cancer cells, other peripheral facts that contribute to the well-being of the patients cannot be taken care of simultaneously. Therefore, the concept of integrated cancer care drew the medical fraternity's attention. The attempt here is to bring Ayurveda under the umbrella of tertiary cancer care to address the RT/CCRT-induced oral complications. This is expected to broaden the scope of essential multimodal and interdisciplinary cancer care.

As per Ayurvedic principles, *Kavala* (gargling) is mentioned as an *Agrya Chikitsa* in *Mukharoga* (disorders of the oral cavity). This easy procedure helps to resolve multitude of difficulties arising in the oral cavity. The *ropana yoga* (healing medicinal recipe), "*Draksha-Guduchyadi kashaya*" in the form of *Kavala* mentioned in the *Ashtanga Hridaya Mukharoga Pratishedha* (management of diseases of the oral cavity), serves the function as a suitable mouthwash in oral side effects of chemo-radiation [6].

Previous studies on alternative systems have primarily focused on single herbs, which may not fully address the various oral side effects of cancer treatment [7–9]. This study is significant as it investigates the efficacy of *Draksha-Guduchyadi Kashaya Kavala*, an herbal combination, in managing oral complications of chemo-radiation.

### 1.2. Objectives

The primary objective of the study is to find out the effectiveness of Ayurvedic mouthwash - *Draksha-Guduchyadi Kashaya*, in reducing the severity of oral side effects of chemo-radiation like mucositis, xerostomia, laryngitis, pharyngitis and pain in terms of onset and intensity.

## 2. Methodology

### 2.1. Trial design

The current study is a concurrent randomized parallel-group study with an allocation ratio 1:1.

### 2.2. Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee of the Institute of Medical Sciences (IMS), Banaras Hindu University (BHU) vide No. Dean/2020/EC/1897 dated 21.1.2020.

### 2.3. CTRI registration of the study

The study was registered at The Clinical Trials Registry- India. (CTRI/2020/04/024672 on 16/04/2020)

### 2.4. Informed written consent

Informed written consent was obtained from each participant before the start of the trial after explaining the study details to the patient.

### 2.5. Drug authentication and accession number

After drug standardization, the drugs were authenticated and deposited in the herbarium of Dept. of Dravyaguna, IMS, BHU and the accession numbers were also provided.

### 2.6. Eligibility criteria for participants

#### 2.6.1. Inclusion criteria

The study included individuals aged 18 to 80, encompassing both males and females, with non-metastatic squamous cell carcinoma in the head and neck region, and the prescribed radiation dose ranged from 60 to 70 Gy, administered over a period of 6–7 weeks in 30–35 fractions.

#### 2.6.2. Exclusion criteria

Patients who had undergone prior RT, pregnant and lactating females, and those unwilling to participate in the study are excluded.

### 2.7. Settings and locations where the data was collected

Patient enrollment was done from the OPD and IPD of Radiotherapy and Radiation Medicine (RT and RM) Department, Sir Sunderlal Hospital, BHU, Varanasi. The study population consisted of patients who registered at the department and were scheduled to undergo radiotherapy with or without chemotherapy.

## 3. Intervention

After inclusion and exclusion criteria, selected patients with indistinguishable morbidity attributes were randomly placed into two equal groups: the intervention group (Ayurveda group) and the control group using a simple randomization technique.

### 3.1. Group 1 - Ayurveda intervention group

The patients in the Ayurveda intervention group were instructed to perform the *kavala* procedure with 50 ml of *Draksha-Guduchyadi kashaya* (details of ingredients in section 1 of supplementary data) as mentioned in *Mukharoga chikitsa* of *Ashtangahridaya* [10] under the supervision of physicians from Ayurveda wing. The *kashaya* (decoction) cooled to normal temperature after preparation was used for *kavala*. *Kavala* should be performed with 50 ml *kashaya* for 2 min, 10 times a day with a time gap of 1.30 h (details in section 2 and 3 of supplementary data), from the first day of treatment up to 6–7 weeks, along with the RT/CCRT and the *kavala* should be continued for the next two months follow up period after RT/CCRT. The detailed timings of the *kavala* are given in section 4 of the supplementary data.

### 3.2. Group 2 - control group

Patients in the control group were advised to use the mouthwash with a solution consisting of sodium bicarbonate and salt (for details, refer to section 5 of supplementary file) against oral side effects with the same amount (50 ml) and with the same duration 2 min, 10 times a day, as in the intervention group. All patients were given general dietary instructions, including a soft and low sugar, low acid diet while avoiding hot and spicy foods, and a recommendation to sip small quantities of water every half hour and maintain oral hygiene using an ultra-soft brush. In addition, all patients were prescribed multivitamin tablets and protein powder. The Ayurvedic intervention was also addressed alongside the guidelines recommended by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) [11]. Patient enrollment began in April 2020 and continued through January 2022, and both groups were thoroughly briefed on the preparation and performance of gargling.

## 4. Outcome

### 4.1. Primary outcome

The major oral complications like mucositis, xerostomia, pharyngitis and laryngitis were assessed with RTOG grading [12] at weekly intervals

of RT/CCRT (6–7 weeks), one month after RT/CCRT, and one month after the first follow-up.

### 4.2. Secondary outcome

The subjective pain changes were assessed using the VAS scale [13] weekly in both groups during radiation and in two follow-ups one month apart. All the gradings were done by a blinded evaluator from the Dept. RT & RM.

## 5. Sample size and sampling technique

The minimum sample size estimated was 60; assuming 15 % lost to follow-up, the required sample size in the present study was set at 70 by taking a 5 % level of significance and 90 % power. After satisfying the inclusion-exclusion criteria, 70 patients were enrolled in the present study, but due to multiple reasons, 10 patients could not turn up for the final assessment. Hence, for the analysis, the data of 60 patients were used. The details are presented in a consort flow diagram in Fig. 1. Patients were selected on a first come basis from the population. In the study, patients were divided into two groups, and the allocation concealment was ensured solely through the use of the lottery method for sampling, facilitating a randomized assignment of participants to the intervention and control groups.

## 6. Blinding

The study was conducted in an open-blinded manner, with a blinded evaluator from the department of RT & RM for grading of outcome variables and the statistical evaluator also being blinded.

## 7. Statistical methods

Data analysis was done by using 'IBM-SPSS-Statistics-20' software. The tables were generated using MS Excel software.

### 7.1. Statistical methods for qualitative variables

Descriptive tables were generated using cross-tabulation with the frequencies and percentages for qualitative variables. The comparisons between the groups were performed by Pearson's Chi-square test.

### 7.2. Statistical methods for quantitative variables

Descriptive statistics were worked out for quantitative parameters, and 'independent *t*-test' was used to compare the measurements between the groups. Non-parametric test such as Mann Whitney-*U* test was used wherever conditions of independent-*t* test were not satisfied. The paired *t*-test was used for comparing the outcome variables within the groups, and the Wilcoxon Signed Rank test was used wherever the conditions of the paired-*t* test were not satisfied.

## 8. Results

### 8.1. Demographic characteristics

Demographic characteristics of all the participants were assessed, and it showed no significant difference between the ages, gender, religion, occupation, socio-economic status, and marital status of patients in the Ayurveda and control groups (details in section 6 of supplementary data).

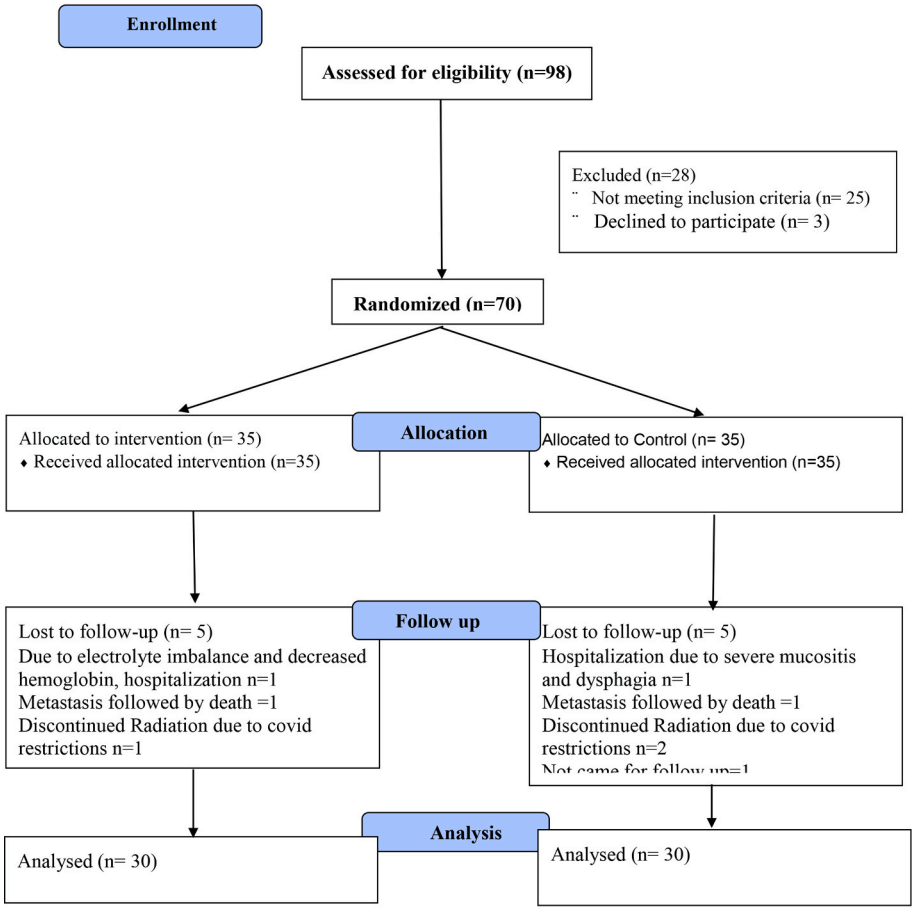


**Fig. 1.** CONSORT flow chart.

### 8.2. Morbidity and individual characteristics

It is observed that 18 patients had tongue cancer, followed by buccal mucosa [17]. More than half of the patients (34) had a differentiated type of HNSCC. 44 patients had either III$^{rd}$ or IV$^{th}$-A stage cancer, and about 41 patients presented ulcerous proliferative growth (UPG) as the dominant presenting complaint that led to the diagnosis of the disease. About 38 patients in both groups received 60 Gy radiations as part of their therapy. Fifty-eight patients were addicted to tobacco use, and no significant difference was observed between the patients of both groups with respect to the above factors (details in section 7 of supplementary data).

### 8.3. Results in response to treatment

#### 8.3.1. Assessment of primary outcome variables

*8.3.1.1. Mucositis.* Data on mucositis had been gathered from all the patients weekly during RT/CCRT and then at two follow-ups with a gap of one month. The details of mucositis grading are given in Table 1.

A week-wise comparison of mucositis between the Ayurveda and control groups shows that when 28 patients did not develop mucositis in the first week in the Ayurveda group, this number is 23 for the control group. This indicates that patients in the control group started developing mucositis early compared to the Ayurveda group. Patients with grade 1 mucositis at the first week of RT/CCRT is only 2 in the Ayurveda group, while the corresponding number in the Control group is 7 in week 1. Similarly, grades at different weeks can be read.

Significant differences were observed between the Ayurveda and Control groups with respect to development of mucositis on weeks 2–7 and on the first follow-up, while the first week and second fllow-up were not significant.

The onset and intensity of mucositis had also been determined to assess the effect of the drug on Ayurveda and control groups and the aggregate of the same is placed in the section 8, Tables 5 and 6 of supplementary data.

*8.3.1.1.1. Onset of mucositis.* The weekly assessment of mucositis showed that when two patients developed mucositis in the first week in the Ayurveda group, seven patients developed the same in the control group. There is a real difference in the second week as 15 patients developed mucositis in the Control group against eight in the Ayurveda group. Gradually, patients in the Ayurveda group also developed Mucositis in the next three weeks. The delay in the onset of mucositis in the Ayurveda group was statistically significant ($p = 0.049$).

*8.3.1.1.2. Intensity of mucositis.* The maximum grade of mucositis has also been derived from the data for each patient. Patients with high-grade mucositis were less in number in the Ayurveda group. When 17 patients experienced grade 3 mucositis in the control group, only one in the Ayurveda group had the same grade mucositis. The number of people who experienced low-grade Mucositis is higher in the Ayurveda group compared to the Control group. Fig. 2 displays the mucositis progression of each patient in the Ayurveda and control groups. There was a highly significant difference between the groups regarding the intensity of Mucositis ($p = 0.000$).

*8.3.1.2. Xerostomia.* Data on xerostomia had been gathered from all the patients weekly during RT/CCRT and then at two follow-ups with a gap of one month. The details of xerostomia grading are given in Table 2.

Week-wise comparison of xerostomia between the Ayurveda and control groups showed that 27 patients did not develop xerostomia in the first week in the Ayurveda group, 25 only in the Control group. In the first week, patients with Grade 1 Xerostomia are three in the Ayurveda group, while the corresponding figure in the Control group is five. Similarly, grades at different weeks can be read.

Significant differences were observed between the Ayurveda and control groups with respect to xerostomia between weeks three to six, while the differences were not statistically significant in the rest of the periods.

The onset and intensity of xerostomia had also been determined to assess the effect of the drug on Ayurveda and control groups and the aggregate of the same is placed in section 9, Tables 7 and 8 of supplementary data.

*8.3.1.2.1. Onset of xerostomia.* The onset of xerostomia is defined as the first appearance of grade 1 xerostomia. It is observed that when three patients developed xerostomia in the first week in the Ayurveda group, five patients developed the same in the control group. This trend is also intact in the second week, with 12 patients in the Control group against eight in the Ayurveda group. Gradually, patients in the Ayurveda group also developed the xerostomia in the next 3 weeks. There is no significant difference in the onset of xerostomia in both groups ($p = 0.505$).

*8.3.1.2.2. Intensity of xerostomia.* The maximum grade of xerostomia has also been derived. When four patients in the Ayurveda group experienced grade 3 xerostomia, ten in the control group went through the same experience. No significant difference is noticed between the two groups in grade 2. When 19 patients experienced grade 2 xerostomia in the control group, 20 in the Ayurveda group had the same grade xerostomia. The number of people who experienced low-grade xerostomia is slightly higher in the Ayurveda group than in the control group. A slightly significant difference between the groups regarding the intensity of xerostomia($p = 0.046$) was found.

*8.3.1.3. Pharyngitis.* Data on pharyngitis had been gathered from all the patients weekly during RT/CCRT and then at two follow-ups with a gap of one month. The details of pharyngitis grading are given in Table 3.

Week-wise comparison of Pharyngitis between the Ayurveda and Control groups shows that 29 patients did not develop Pharyngitis in the first week in the Ayurveda group and 25 in the Control group. In the first week, only one patient had Grade 1 Pharyngitis in the Ayurveda group, while in the Control group, five patients had Grade 1 Pharyngitis. Similarly, grading at different weeks can be read. Significant differences

**Table 1**
Change in Mucositis status.

| Group | Change in Grade | Mucositis Number of patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **WK 1** | **WK 2** | **WK3** | **WK 4** | **WK 5** | **WK 6** | **WK 7** | **F 1** | **F 2** |
| Group 1 -Ayurveda | **0** | 28 | 18 | 15 | 7 | 9 | 18 | 25 | 29 | 29 |
| | **1** | 2 | 12 | 12 | 16 | 13 | 11 | 4 | 1 | 1 |
| | **2** | 0 | 0 | 3 | 6 | 8 | 1 | 1 | 0 | 0 |
| | **3** | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | **4** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Group 2 - Control | **0** | 23 | 8 | 1 | 0 | 0 | 0 | 0 | 10 | 29 |
| | **1** | 7 | 17 | 12 | 6 | 5 | 6 | 12 | 18 | 1 |
| | **2** | 0 | 5 | 14 | 15 | 14 | 15 | 18 | 2 | 0 |
| | **3** | 0 | 0 | 3 | 9 | 11 | 8 | 0 | 0 | 0 |
| | **4** | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| Between the group comparison Mann-Whitney *U* test | | z = 1.793 P = 0.073 | z = 2.965 P = 0.003 | z = 4.561 P = 0.000 | z = 4.432 P = 0.000 | z = 4.971 P = 0.000 | z = 6.189 P = 0.000 | z = 6.393 P = 0.000 | z = 5.076 P = 0.000 | z = 0.000 P = 1 |

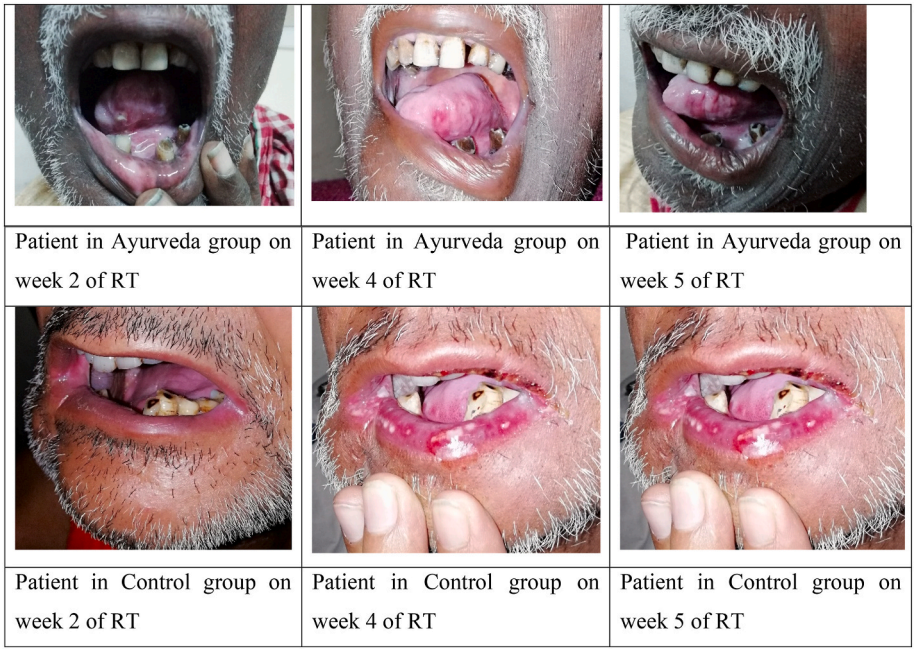


**Fig. 2. The mucositis progression of each patient in the** Ayurveda **group and control group.**

**Table 2**
Change in Xerostomia status.

| Group | Change in Grade | Xerostomia Number of patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **WK 1** | **WK 2** | **WK3** | **WK 4** | **WK 5** | **WK 6** | **WK 7** | **F 1** | **F 2** |
| Group 1 | 0 | 27 | 19 | 5 | 1 | 0 | 0 | 3 | 6 | 7 |
| Ayurveda | 1 | 3 | 10 | 25 | 24 | 16 | 14 | 18 | 17 | 22 |
| | 2 | 0 | 1 | 0 | 5 | 11 | 16 | 8 | 7 | 1 |
| | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 |
| | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Group 2 Control | 0 | 25 | 14 | 2 | 0 | 0 | 0 | 0 | 3 | 3 |
| | 1 | 5 | 15 | 20 | 14 | 8 | 5 | 18 | 17 | 24 |
| | 2 | 0 | 1 | 8 | 16 | 17 | 22 | 11 | 10 | 3 |
| | 3 | 0 | 0 | 0 | 0 | 5 | 3 | 1 | 0 | 0 |
| | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Between the group comparison | | z = −0.753 | z = −1.228 | z = −2.829 | z = −3.032 | z = −1.977 | z = −2.781 | z = −1.202 | z = −1.171 | z = −1.623 |
| Mann-Whitney *U* test | | P = 0.451 | P = 0.219 | P = 0.005 | P = 0.002 | P = 0.048 | P = 0.005 | P = 0.229 | P = 0.242 | P = 0.105 |

**Table 3**
Change in Pharyngitis status.

| Group | Change in Grade | Pharynx Number of patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **WK 1** | **WK 2** | **WK3** | **WK 4** | **WK 5** | **WK 6** | **WK 7** | **F 1** | **F 2** |
| Group 1 | 0 | 29 | 20 | 7 | 3 | 1 | 2 | 4 | 12 | 25 |
| Ayurveda | 1 | 1 | 10 | 16 | 17 | 18 | 21 | 17 | 14 | 5 |
| | 2 | 0 | 0 | 7 | 10 | 11 | 5 | 6 | 4 | 0 |
| | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 |
| | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Group 2 Control | 0 | 25 | 10 | 0 | 0 | 0 | 0 | 1 | 5 | 20 |
| | 1 | 5 | 19 | 20 | 3 | 2 | 3 | 13 | 22 | 8 |
| | 2 | 0 | 1 | 10 | 23 | 19 | 21 | 10 | 3 | 2 |
| | 3 | 0 | 0 | 0 | 4 | 9 | 6 | 6 | 0 | 0 |
| | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Between the group comparison | | z = −1.707 | z = −2.625 | z = −1.950 | z = −4.630 | z = −4.943 | z = −4.756 | z = −2.010 | z = −1.391 | z = −1.569 |
| Mann-Whitney *U* test | | t = 0.088 | t = 0.009 | t = 0.051 | t = 0.000 | t = 0.000 | t = 0.000 | t = 0.044 | t = 0.164 | t = 0.117 |

were observed between the Ayurveda and Control groups regarding Pharyngitis on Weeks 2, 4 to 7, while the remaining periods were not significant.

The onset and intensity of pharyngitis had also been determined to assess the effect of the drug on Ayurveda and control groups. Details are given in section 10, Tables 9 and 10 of supplementary data.

*8.3.1.3.1. Onset of pharyngitis.* The weekly assessment of pharyngitis shows that when only one patient developed pharyngitis in the first week in the Ayurveda group, five patients developed the same in the control group. This trend is also intact in the second week, with 14

patients in the control group against 9 in the Ayurveda group. Gradually, patients in the Ayurveda group also developed pharyngitis in the next three weeks. The delay in the onset of pharyngitis in the Ayurveda group was statistically significant compared to the control group ($p = 0.034$).

*8.3.1.3.2. Intensity of pharyngitis.* The maximum grade of pharyngitis has also been derived from the data for each patient. Patients with grade 4 pharyngitis were absent in both groups. Fourteen patients experienced grade 3 Pharyngitis in the control group compared to four in the Ayurveda group. It was found that there was a significant difference between the groups for the intensity of pharyngitis($p = 0.002$).

*8.3.1.4. Laryngitis.* Data on laryngitis had been gathered from all the patients weekly during RT/CCRT and then at two follow-ups with a gap of one month. The details of grading are given in Table 4.

Week-wise comparison of laryngitis between the groups shows that 29 patients did not develop laryngitis in the first week in the Ayurveda group and 28 in the Control group. In the first week, patients with grade 1 Laryngitis are one in the Ayurveda group, while the corresponding figure in the control group is two. Similarly, grades at different weeks can be read. Significant differences were observed between the Ayurveda and Control groups concerning laryngitis from weeks 3 to follow-up 1, while the remaining periods were not significant.

The onset and intensity of laryngitis had also been determined to assess the effect of the drug on Ayurveda and control groups; the details are given in section 11, Tables 11 and 12 of supplementary data.

*8.3.1.4.1. Onset of laryngitis.* The onset of laryngitis is defined as the first appearance of grade 1 laryngitis. It is observed that when only one patient developed laryngitis in the first week in the Ayurveda group, two patients developed the same in the control group. This trend was also intact through the second week, with seven patients in the control group against two in the Ayurveda group developing laryngitis. In the third week, 12 patients in the control against 9 in the Ayurveda group developed laryngitis. Gradually, patients in the Ayurveda group also developed laryngitis in the next three weeks. The delay in the onset of laryngitis in the Ayurveda group was statistically significant compared to the Ayurveda group ($p = 0.009$).

*8.3.1.4.2. Intensity of laryngitis.* The maximum grade of laryngitis had also been derived from the data. Patients with high grade 4 laryngitis were absent in both groups. However, a difference is noticed between the groups in grade 3. When four patients experienced grade 3 laryngitis in the control group, two in the Ayurveda group had the same grade laryngitis. The number of people who experienced grade 2 laryngitis in the control Group is 15, but the same is only six in the Ayurveda group. Low-grade laryngitis is more in the Ayurveda group than in the control group. There was a significant difference between the groups regarding the intensity of laryngitis ($p = 0.035$).

*8.3.2. Assessment of secondary outcome variable-pain*

Grading of pain based on the VAS scale reveals significant differences between the Ayurveda and control groups on all weeks and during the first follow-up. The details of pain assessment are given in Table 5.

In the initial weeks, the mean pain scores were less in both groups, they peaked in the fifth week and gradually reduced and became insignificant at the second follow-up.

Since the onset of pain was there in both groups from week one onwards, only the details of the intensity of pain had been determined to assess the effect of the drug on Ayurveda and control groups.

*8.3.3. Intensity of pain*

The maximum grade of pain has been derived from the data for each patient, and the aggregate of the same is placed in section 12, table 13 of supplementary data.

Nine patients experienced pain of grade 5 and above in the Ayurveda group. In the control group, the corresponding figure is 28. There was a highly significant difference between the groups in pain intensity ($p = 0.000$).

## 9. Discussion

The present study aims to assess the effect of *'Draksha-Guduchyadi Kashaya Kavala'* on oral complications of RT/CCRT. The study topic was selected based on the immense potential of Ayurvedic principles and formulations to satisfy the unmet needs of cancer patients and thereby increase the quality of life and aid in the completion of existing treatment of cancer patients.

In radiation induced complications, high energy radiation serves as *Teekshna Agantu Nidana* (strong external aetiology), which causes the *Bodhaka Kapha* (one of the subtypes of *Kapha* situated on the tongue) vitiation and results in *Asraya Dhathu Nasha* (diminution of *Dhathu*), i.e., desquamation and basement membrane damage along with loss of the protective barrier. This then leads to localized *Vata* and *Pitta* vitiation and results in *Mukhantargatha Vrana* (ulcer in the oral cavity). *Doshik* appreciation of symptoms can be seen as *Daha* (burning sensation), *Raga* (redness), *Paaka* (suppuration) due to vitiated *Pitta*; *Rookshatha* (dryness), *Ruja* (pain), *Dourbalya* (weakness) due to vitiated *Vata*; *Gourava*, (heaviness), *Anna Dwesha* (aversion to food) due to vitiated *Kapha*. The difficulties associated with *Sarva Sara Mukhapaka* (inflammation of the entire oral cavity) may then extend to *Oshta* (lips), *Jihva* (tongue), *Dantha* (teeth), *Danthamoola* (root of teeth), *Gala* (throat) etc. It later causes difficulty in opening the mouth. This will affect the food intake and thereby cause impaired production of *Rasa* (primary product of digested food) and the subsequent *Dhathus* (structural components of the body). As a result, the entire body system may get affected, and *Ojas* (the essence of all seven *Dhathus*) may get impaired if left untreated.

### 9.1. Probable mode of action of the trial drug

The inflammatory response in oral mucosa, larynx, and pharynx,

**Table 4**
–Change in Laryngitis status.

| Group | Change in Grade | Laryngitis Number of Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **WK 1** | **WK 2** | **WK3** | **WK 4** | **WK 5** | **WK 6** | **WK 7** | **F 1** | **F 2** |
| Group 1 | **0** | 29 | 27 | 18 | 19 | 8 | 5 | 14 | 23 | 27 |
| Ayurveda | **1** | 1 | 2 | 10 | 8 | 19 | 20 | 10 | 5 | 3 |
| | **2** | 0 | 1 | 2 | 3 | 3 | 4 | 5 | 2 | 0 |
| | **3** | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| | **4** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Group 2 Control | **0** | 28 | 22 | 9 | 3 | 1 | 2 | 8 | 13 | 24 |
| | **1** | 2 | 8 | 15 | 15 | 19 | 15 | 8 | 12 | 5 |
| | **2** | 0 | 0 | 6 | 11 | 7 | 12 | 12 | 5 | 1 |
| | **3** | 0 | 0 | 0 | 1 | 3 | 1 | 2 | 0 | 0 |
| | **4** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Between the group comparison | | **z = -0.587** | **z = -1.563** | **z = -2.428** | **z = -4.203** | **z = -3.029** | **z = -2.233** | **z = -2.103** | **z = -2.553** | **z = -1.110** |
| Mann-Whitney *U* test | | **p = 0.557** | **p = 0.118** | **t = 0.015** | **t = 0.000** | **t = 0.002** | **t = 0.026** | **t = 0.036** | **t = 0.011** | **t = 0.267** |

**Table 5**
Pain VAS score.

| | Pain VAS Score Mean ± SD | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **WK 1** | **WK 2** | **WK 3** | **WK 4** | **WK 5** | **WK 6** | **WK 7** | **F 1** | **F 2** |
| Group 1 (Ayurveda) | 0.53 ± 1.252 | 0.87 ± 1.479 | 1.40 ± 1.923 | 1.80 ± 1.606 | 2.37 ± 1.712 | 1.93 ± 2.016 | 1.37 ± 1.810 | 0.27 ± 0.640 | 0 ± 0 |
| Group 2 (Control) | 1 ± 1.017 | 2.17 ± 1.177 | 3.53 ± 1.252 | 4.6 ± 1.102 | 5.4 ± 1.133 | 4.17 ± 0.950 | 3.90 ± 1.269 | 1.13 ± 0.819 | 0.10 ± 0.305 |
| Between the Groups | Z = −2.643 | Z = −3.876 | Z = −4.375 | Z = −5.557 | Z = −5.625 | Z = −4.148 | Z = −4.827 | Z = −4.409 | Z = −1.762 |
| (Mann-Whitney *U* Test) | t = 0.008 | t = 0.000 | t = 0.000 | t = 0.000 | t = 0.000 | t = 0.000 | t = 0.000 | t = 0.000 | t = 0.078 |

caused partly by oxidative stress and inflammation, are common side effects of RT/CCRT [14]. Anti-inflammatory plant-derived and other natural therapies have recently been shown to help control radiation-induced inflammations. There has been an increase in interest in natural-based agents in recent years due to the adverse effects of chemical medications. Natural items can reduce or prevent inflammatory changes in the oral cavity caused by chemotherapy and radiation therapy.

*Draksha-guduchyadi kashaya*, an Ayurvedic formulation prescribed as *Kavala* (gargling), can resolve difficulties arising in the *Manya* (neck), *Sira* (head), *Karna* (ear), *Mukha* (oral cavity), and *Netra* (eyes). It reduces *Praseka* (salivation), *Kanthamaya* (diseases of the throat), *Pinasa* (catarrh/chronic rhinitis), *Vaktra Sosha* (dryness of the mouth), and *Aruchi* (tastelessness). In addition to the clinical efficacy of the drug, it is worth noting that the technique of *Kavala* is the best *Upakrama* (therapeutic method) in *Mukharoga* (oral diseases) according to classical texts [15].

Among four varieties of *Kavala, Ropana Kavala* (healing type of gargle) is found to be the best against the mentioned condition. The overall actions of drugs in *Draksha-guduchyadi yoga* have *Sita Virya* (cold potency), *Kashaya Tiktha Rasa* (astringent, acrid taste), and *Madhura Vipaka* (biotransformed sweet taste). All these properties of the *yoga* impart '*Pitta pradhana tridosa shamana*' quality that allows simultaneous *Ropana* (healing) and *Shamana* (palliative) actions [6]. Understandably, the trial drug's ability to heal wounds quickly lowered the severity of all inflammations [6]. This treatment-based procedure, which is repeated every 1.5 h, stimulates the main and accessory salivary glands. This action lowers xerostomia, fungal and other microbial contamination by creating more saliva, which further aids in swallowing and articulation of voice, etc. This repetitive practice is based on the text *Sarngadhara Samhitha* [16]. Moreover, the pressure created during the swishing movement helps to remove the debris in the oral cavity and thereby reduces the harmful oral microbiota. As the patients of HNC undergoing RT/CCRT are unable to open their mouth properly due to pain and muscular stiffness, brushing, and other oral hygiene measures will be less. Hence, repeated *Kavala* will provide benefits of oral hygiene by minimizing the growth of harmful bacteria and fungi along with preventing or reducing the severity of inflammatory responses.

The use of honey as *Anupana* (co-administer with medicine) helped in greater absorption and penetration of the trial drug because of its *Yogavahitwa* property (takes the properties of other substances along with its property). The thin mucosal membrane and penetrative power of honey aid in faster absorption and action of drugs. Multiple studies have proved the effectiveness of honey alone in this condition [17]. Honey reduces *Candida* and aerobic pathogenic bacterial infections, thereby promoting weight gain, delaying the onset of oral mucositis, and reducing pain [18].

The drugs in the yoga possess qualities like *Mukharoga Hara* (subsiding oral diseases), *Rasayana* (rejuvenation), *Vedhana Sthapana* (analgesic), *Sulahara* (pain relieving), *Daha Hara* (cures burning), *Kasa Hara* (cough relieving), *Swarya* (beneficial for voice), *Kantya* (beneficial for throat), *Rakta-pitta Shamana* (subsiding *Rakta-pitta*), *Trishna Hara (subsiding thirst), Vrana Hara (subsiding ulcer/wound), Vrana Ropana* (ulcer/wound healing), etc. [19,20], which help to tackle the difficulties arising out of RT/CCRT.

### 9.2. Contemporary pharmacological properties of the drug

Almost all the drugs possess anti-oxidant, anti-microbial, anti-inflammatory, and analgesic action. Herbal drugs used in this study helped to reduce oxidative stress to a great extent. If oxidative stress is relieved, the major cause of inflammation is reduced, and the anti-inflammatory action gives added benefit. This itself reduces inflammation, and gradually, the wound heals. The medicines also possess fast wound healing properties, especially *Draksha, Jati*, and *Triphala* [21–23].

The body's antioxidant response can handle increased oxidative damage in sick states up to a certain point, but beyond that point, extra antioxidants are needed to counteract the increased stress [24]. Naturally occurring tocotrienols, which are similar to Vitamin E, found in vegetable oil may be useful in cancer therapy by making cancer cells more vulnerable to chemotherapeutic drugs [25]. Tocotrienol prevents 5-fluorouracil-induced reactive oxygen species (ROS) production in oral keratinocytes via stabilizing nuclear factor erythroid 2-related factor 2 (Nrf2), a redox-sensitive transcription factor [26]. Vitamin C, Vitamin E, etc. constitute the non-enzymatic defence against oxidative damage [24]. Ayurvedic drugs like *Amalaki, Hareetali, Vibeetaki Draksha*, etc. [27], possess Vitamin E and C to a greater extent.

A multitude of research on *Triphala* indicates that the formula may be helpful for several clinical applications, including appetite stimulation, reduction of hyperacidity, antioxidant, anti-inflammatory, immunomodulating, antibacterial, antimutagenic, adaptogenic, hypoglycemic, anti-neoplastic, chemoprotective, radioprotective effects, and prevention of dental caries [28]. Similar kinds of action are seen in other drugs also. The above qualities of drugs not only prevent or lessen the severity of the side effects of RT/CCRT, but they also give immunogenic and adaptogenic properties that will help improve the quality of life and give the body more strength to handle the very strong cancer treatment.

Patients could also eat and drink better following *Kavala* since they could open their mouths without trouble. At the same time, patients who used the soda-salt mouthwash made less progress in reducing oral adverse effects, particularly mucositis. Furthermore, the solution's scorching taste rendered it unappealing to patients. However, it is an easily available and less costly method that helps to reduce oral difficulties to an extent. Apart from the cost-effectiveness, all other parameters favour the *Draksha guduchyadi Kavala yoga* against oral complications of RT/CCRT.

### 9.3. Compliance to Kavala

As per the patients' feedback, the execution of the *Kavala* procedure ten times a day seems relatively easy. The guidelines for the soda salt mouthwash align with similar timeframes, eliminating any grievances regarding the *kavala's* scheduling. Nevertheless, the preparation of *kashaya* demands considerable time and necessitates specific amenities. As many patients receive treatments away from their residences, organizing the required facilities for boiling the *kashaya* becomes an additional task. This predicament could be effectively addressed by introducing ready-to-use formulations in the form of powders or *Arkas* (herbal distillate), which requires further studies to explore their practical application and efficacy.

### 9.4. Limitation of the study

A two-month follow-up may not provide sufficient data to evaluate the long-term effectiveness of the drug. Additionally, the anti-inflammatory effects of the drug were not objectively measured. Variability in outcome variables may have occurred due to including HNC patients with different anatomical sites. Finally, the smaller sample size may limit the generalizability of the study's findings to a larger patient population.

## 10. Conclusion

Ayurvedic mouthwash *'Draksha-guduchyadi kashaya Kavala'* significantly delayed the onset of mucositis, pharyngitis, and laryngitis in patients undergoing RT/CCRT. The onset of xerostomia and pain had no significant difference between the groups. Additionally, the treatment effectively reduced the intensity of various oral complications without any observed side effects. Thus, helped the patient maintain the nutritional requirement and successfully complete the treatment course with minimum adverse effects. This study highlights the potential of Ayurvedic formulations as an affordable alternative to existing methods in managing oral complications of RT/CCRT. By integrating Ayurveda interventions, patients can receive a comprehensive care that addresses a broader range of health concerns.

## Author contributions

**S C K**: Conceptualization, Methodology, Investigation, Data curation, Writing- Original draft, Visualization, Project administration, Funding acquisition. **M V R**: Validation, Investigation, Resources, Visualization, Writing- Reviewing and Editing. **R P:** Validation, Investigation, Resources, Visualization, Supervision. **S C**: Methodology, Investigation, Resources, Writing – review and editing, Visualization, Supervision, Project administration. **O P S**: Validation, Formal analysis, Data curation, Resources, Visualization, Supervision, Project administration. **K S D:** Conceptualization, Study design, Formal analysis, Resources.

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## Declaration of competing interest

None.

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## Appendix A. Supplementary data

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