ISSN: 2476-2377

Research Article

International Journal of Cancer Research & Therapy

The Efficacy of Curcumin Mouthwash in Coconut Oil Solvent for Preventing Oral Mucositis in Locally Advanced Head and Neck Cancer Patients Undergoing Concurrent Chemoradiotherapy

Jakkapan Rongmuang[1], Patrapim Sunpaweravong[1], Arunee Dechaphunkul[1], Manupol Tangthongkum[2], Panupong Puttarak[3], Apinya Prisutkul[1] and Chirawadee Sathitruangsak[1]*

[1]Holistic Center for Cancer Study and Care (HOCC-PSU) and Medical Oncology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Thailand

[2]Division of Otolaryngology, Faculty of Medicine, Prince of Songkla University, Thailand

[3]Department of Pharmacognosy and Pharmaceutical Botany, Prince of Songkla University, Thailand

***Corresponding Author**
Chirawadee Sathitruangsak, Medical Oncology Unit, Division of Internal Medicine, Prince of Songkla University, Thailand

Submitted: 2023, Apr 15; **Accepted**: 2023, May 16 **Published**: 2023, May 19

Citation: Sathitruangsak, C., Sunpaweravong, P., Dechaphunkul, A., Tangthongkum, M., Puttarak, P., et al. (2023). The Efficacy of Curcumin Mouthwash in Coconut Oil Solvent for Preventing Oral Mucositis in Locally Advanced Head and Neck Cancer Patients Undergoing Concurrent Chemoradiotherapy. *Int J Cancer Res Ther, 8*(2), 34-45.

Abstract

***Background**: To evaluate the efficacy and safety of curcumin mouthwash in preventing and relieving CCRT-induced severe oral mucositis*

***Methods**: We conducted a blinded, randomized controlled trial in patients with head and neck cancer receiving definite CCRT with 3-weekly cisplatin. Eligible patients were randomly assigned to receive curcumin mouthwash (MW) or normal saline solution (NSS) MW.*

***Results**: Thirty patients were enrolled in this study. Ten patients in the curcumin MW group and 13 patients in the NSS MW group were analyzed. The incidence of severe oral mucositis (grade 3–4 defined by the WHO grading scale) was reduced in the curcumin MW group at weeks 4, 7, and 10. However, it was not statistically different. The severity of oral mucositis was significantly reduced in the curcumin MW group at week 4 (mean = 0.09 vs 0.32, p = 0.016). There was no significant toxicities or safety concerns for curcumin MW.*

***Conclusions**: The incidence and severity of oral mucositis trend to decreased in curcumin MW group compared with the NSS MW group. These results indicated the feasibility and acceptability for curcumin MW in locally advanced head and neck cancer patients undergoing CCRT.*

Keywords: Head and Neck Cancer, Oral Mucositis, Curcumin Mouthwash, Chemoradiotherapy

1. Introduction

Oral mucositis is a common and serious complication in patients receiving concurrent chemo-radiotherapy (CCRT) for head and neck cancer. Oral mucositis represents a major nonhematologic complication of CCRT and is associated with significant morbidities, such as pain, odynophagia, subsequent dehydration, and malnutrition. Severe oral mucositis can also compromise the delivery of optimal anticancer therapy, resulting in dose reduction or treatment interruption. These disruptions negatively treatment outcome and patient survival [1,2]. The incidence of severe oral mucositis (grade 3–4 defined by the WHO grading scale) varies among studies, ranging from 30–80% depending on the regimen and dose of cisplatin, the primary site of the cancer, type, and total dose of radiation [2-6].

There is no uniformly effective therapy for preventing radiation-related oral mucositis, thus, treatment is essentially palliation. Traditional management consists of using topical anesthetics and/

or anti-inflammatory drugs (e.g., lidocaine, diphenhydramine) or agents such as colloidal silver solutions, salt and soda rinses, or hydrogen peroxide rinses. It also includes management of hydration, nutritional support, systemic pain relief, infection surveillance and treatment [7]. However, there is no clear evidence that these interventions significantly affect oral mucositis [8]. Currently, there is a strategy to reduce or prevent its occurrence with chemoradioprotectors. Three substances show positive clinical effects including amifostine, palifermin, and RRx-001 [9].

The main limitation, however, is that these agents are not widely available in clinical practice. Phytochemicals have attracted the attention of researchers in the field of medicine. Curcumin, an extract of turmeric, has been extensively studied for its various therapeutic properties including antioxidant, analgesic, anti-inflammatory, antitumoral, antimicrobial, antiseptic, chemosensitizing, and radiosensitizing effects [10-12]. Curcumin has been evaluated in several studies and shown efficacy in terms of rapid wound healing and better patient compliance compared with chlorhexidine mouthwash for the management of radio-chemotherapy induced oral mucositis [13].

No oral or systemic complications were reported. Recent study showed the efficacy of using 0.1% curcumin mouthwash to delay the onset of radiation-induced oral mucositis but not prevent or reduce the severity [14]. Various clinical trials have been conducted to test the efficacy of curcumin in reducing incidence of oral mucositis, but the strong evidence is still lacking [13-15]. Curcumin exhibits poor solubility in water. As a liposoluble compound, curcumin can be extracted from turmeric rhizomes with organic solvents [16]. Therefore, edible oils have been used as a solvent [17,18]. In this pilot study, we primarily aim to explore the feasibility of curcumin MW in coconut oil solvent in locally advanced head and neck cancer patients undergoing CCRT. The secondary objective was to determine the efficacy of the curcumin MW in coconut oil solvent for preventing and relieving oral mucositis.

2. Materials and Methods

2.1 Subjects

We conducted an investigator-blinded, pilot prospective randomized controlled trial at in the Medical Oncology Unit, Songklanagarind hospital, Prince of Songkla University, Thailand, during October 2020 to December 2020. The eligibility criteria were as follows: patients who were histologically diagnosed with head and neck cancer; age ≥ 18 years; undergoing CCRT with 3-weekly high-dose cisplatin (minimum RT dose of 50 Gy); Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; adequate organ function, bone marrow function (neutrophil count ≥ 1.5 x 10^9/L, hemoglobin ≥ 8 g/dl, platelet count ≥ 100 x 10^9/L), renal function (creatinine clearance ≥ 60 ml/min/1.73m^2), and liver function (transaminase ≤ 1.5 UNL, AST/ALT < 2. 5–3 ULN). Patients were excluded if they had prior induction chemotherapy; were exposed to prior radiotherapy in the head and neck area; known hypersensitivity to study drugs; pregnancy or lactating women; inability to communicate or comply with all study requirements; using any prophylactic or therapeutic mouthwash; had oral surgery within the previous 6 weeks; poor oral hygiene or xerostomia; comorbidities (poorly controlled diabetes mellitus, hypertension, schizophrenia, bipolar disorders, severe depression); or participation in other ongoing clinical trials.

The study protocol was approved by the local ethics committee on Human Research (Ref No. REC 63-138-14-1) of the Faculty of Medicine, Prince of Songkla University, Thailand. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent.

2.2 Study Procedures

All patients who met the eligibility criteria were randomized using opaque envelopes to either curcumin MW (arm A) or NSS MW (arm B) in a 1:1 ratio. A statistician monitored the computerized randomization. The sealed dark brown opaque envelopes used for randomization contained a card folded four times, labeled A or B, and were assigned to the respective arms. At the beginning of the study, all patients were confirmed to have no tooth infections or ulcers in the oral cavity. Curcumin MW was prepared under the expertise of the Department of Pharmaceutics, College of Pharmacy. Curcumin solutions were prepared using 5 g of standard curcumin powder (orangish-yellow colored powder) available from the Pharmacy Division, Songklanagarind Hospital, and dissolved in 100 ml of coconut oil continuously for 24 hours, filtered, and bottled. Five grams of curcumin powder yields Curcuminoids at approximately 20 µg/ml, which is the amount adapted from the curcumin capsule certificates.

The mouthwash was then tested for contamination in accordance with the criteria of Thai herbal pharmacopoeia by the Scientific Instrument Center, Prince of Songkla University. The amount of essential substances including Curcuminoids was analyzed by HPLC, to verify that the solution contained Curcuminoids at a concentration of at least 20 µg/ml. The patients were treated with the prepared curcumin mouthwash 5% w/v or NSS mouthwash by an unblinded oncology nurse. All patients were instructed to swish15 ml of the test solutions (curcumin MW or NSS MW) for one minute, four times daily during the CCRT period. Patients were instructed to begin using the mouthwash from the first day of radiation.The patients were trained by a physician to swish the oral cavity and expectorate in the presence of an attentive primary caregiver with instructions to adhere to the procedure as specified. They were also requested to swish after food intake and abstain from eating for 30 min after use.

Anticancer therapy included RT 70 Gy/35 fractions over 7 weeks with high dose cisplatin injection of 80–100 mg/m^2 every 3 weeks for a total of 3 cycles as shown in Figure 1.

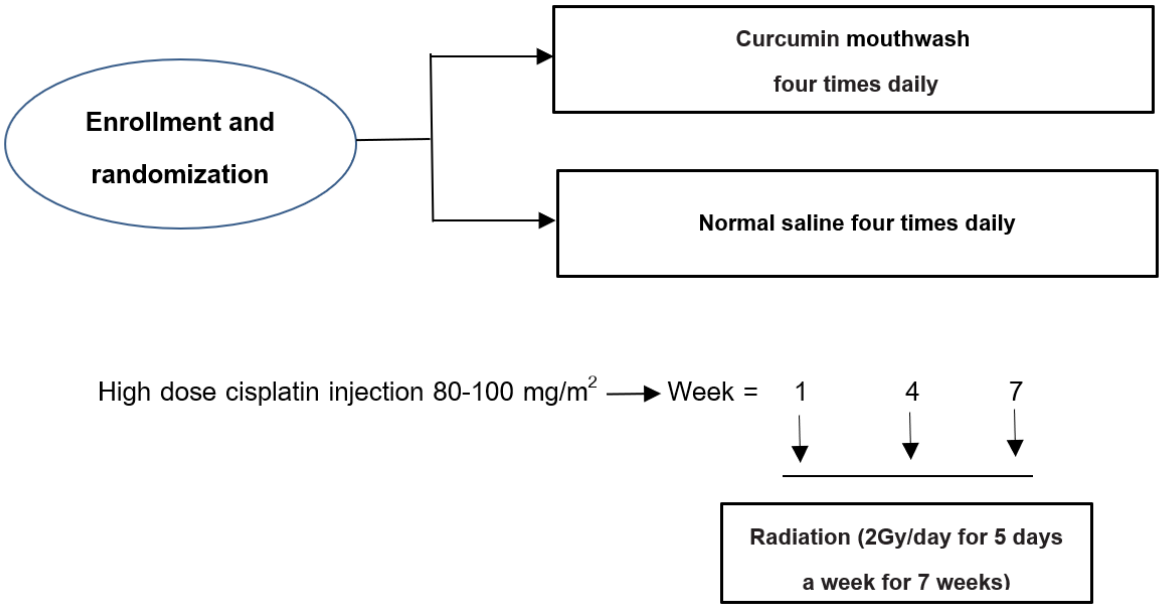

Figure 1: Schedule of chemoradiotherapy and oral treatment

Treatment was administered during and two weeks after completion of radiotherapy. Study evaluation was conducted before radiotherapy and routinely after for up to 3 weeks following the completion of anticancer therapy. Oral mucositis was assessed using the WHO oral mucositis grading scale and the New scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy before the start, during (week 2, 4, and 7), and at the end (week 10) of treatment [19,20]. We defined week 1 as the first date of CCRT. A deviation of ±2 days for oral mucositis evaluation was permitted.

The patients were followed as scheduled. Oral mucositis was assessed at each follow-up visit independently by two calibrated investigators unaware of the treatment. The first investigator used the WHO oral mucositis grading scale, whereas the second investigator used the New scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. An unblind oncology nurse recorded any side effects from the mouthwash at each follow-up visit.

Standard oral, dental, medical, and supportive care was provided to all patients. The patients were instructed to clean their teeth with a soft toothbrush four times a day. If spontaneous gum bleeding occurred, they could swish with the study mouthwash instead to avoid aggravating the injury with a toothbrush. A feeding tube was placed only when it was needed. Oral cavity smears for microbiological testing were collected only in patients with a suspicion of local infection, and antimicrobials (antibiotics and antifungal agents) were administered only after a culture sensitivity test. Additionally, rinsing with analgesic solutions was prescribed if required, such as a 2% lidocaine HCl viscous solution. All patients were given dietary counseling and were recommended dietary supplements (protein-enriched powders) to meet their nutritional requirements.

2.3 Outcomes

The primary endpoint for the curcumin MW was safety, feasibility, and acceptability. The secondary endpoints were the incidence of severe oral mucositis (grade 3–4 defined by the WHO grading scale), the severity of oral mucositis defined by the WHO oral mucositis grading scale and the New scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy.

2.4 Study tools and outcome measurement

The objective of the assessment was to monitor oral changes resulting from CCRT by monitoring oral cavity structure and function. Assessment was divided into the degree of impact that occurs, such as atrophy, redness, swelling, and ulceration, and the effects of inflammation, such as pain and eating [21]. The tools we choose to evaluate the oral mucosa include the WHO oral mucositis grading scale and the New scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy (see appendix). Pain score was recorded using a 10-point scale, the Numerical Rating Scale (NRS), defined as follows: 0 = no pain and 10 = worst possible pain [22]. Compliance was monitored by a self-recorded book. Finally, patients with less than 80% of mouthwash compliance were removed from the study.

This study used the WHO oral mucositis grading scale as the primary evaluation tool, which is widely used in practice and clinical trials. We also used the New scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy as a secondary tool. This secondary

tool provides a higher quality and more detailed measurement by carefully evaluating 9 locations in the mouth. We anticipate that it will be easier to differentiate severe oral mucositis using this precise tool. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [23].

2.5 Sample Size

We estimated that the incidence of severe oral mucositis (grade 3–4 defined by the WHO grading scale) was 65% based on the study of Anderson [4]. The incidence of severe grade oral mucositis (grade 3–4 defined by the WHO grading scale) was 65% in the placebo arm. The 20% difference represents the hypothesis that when adding curcumin MW, severe oral mucositis will reduce from 65% to 45%. Therefore, a sample size of 192 patients, 96 in each arm, was determined to be sufficient to detect a clinically significant difference of 20% between groups using a two-tailed z-test of proportions between two groups with 80% power and a 5% level of significance. However, in this pilot study, we determined the acceptability and feasibility of curcumin MW in 30 patients with locally advanced head and neck cancer who underwent CCRT with cisplatin.

2.6 Statistical Analysis

All statistical analyses were performed with the R program, version 4.0.4 [24]. Chi-square and Fisher's exact test were used to measure differences in creatinine elevation and adverse events between the two groups. P-values < 0.05 were considered statistically significant.

3. Results

3.1 Patient Background

From October of 2020 to December of 2020, 30 patients were enrolled in the study. Three patients in the study group and one patient in the control group were in poor compliance with less than 80% mouthwash use. Two patients in the study group were changed to palliative treatment. One patient in the control group participated in another clinical trial. Thus, 23 patients were available for the analysis (Figure 2).

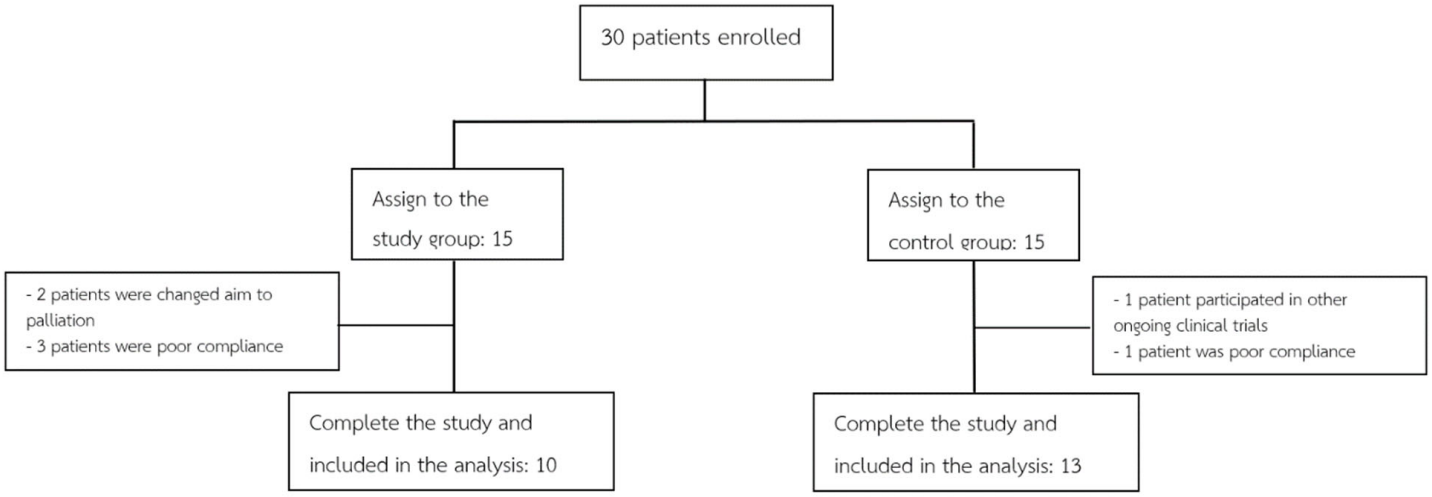

Figure 2: Consort diagram for the study

3.2 Demographic characteristics of the study participants

Baseline characteristics are shown in Table 1. Patient mean age in the curcumin MW group and the NSS MW group was 57 and 60 years, respectively ($p = 0.456$). The majority of the patients were male, with a performance status of 1, a history of smoking and alcohol drinking, and diagnosed with locally advanced disease. The baseline characteristics were well balanced between the two groups, except more patients in the NSS MW group had primary nasopharynx cancer (1 patient in curcumin MW group and 4 patients in NSS MW group), although this was not statistically significant.

Variables		Curcumin MW (N = 10)	NSS MW (N = 13)	P-value
Gender, n (%)				0.604
	Male	9 (90)	10 (77)	
Age				0.456
	Mean ± SD	57±9.8	60±9.1	
ECOG, n (%)				1.00
	0	1 (10)	1 (8)	
	1	9 (90)	12 (92)	
Site, n (%)				0.607
	Oral cavity	2 (20)	1 (8)	
	Oropharynx P16 positive P16 negative Unknown	3 (30) 0 3 0	3 (23) 1 1 1	
	Hypopharynx	2 (20)	1 (8)	
	Nasopharynx	1 (10)	4 (30)	
	Glottic larynx	2 (20)	1 (8)	
	Supraglottic larynx	0 (0)	2 (15)	
	Maxillary sinus	0 (0)	1 (8)	
TNM staging, n (%)				
	Primary			0.125
	T2	1 (10)	3 (23)	
	T3	6 (60)	2 (15)	
	T4	3 (30)	8 (62)	
	Regional node			0.798
	N0	2 (20)	1 (8)	
	N1	1 (10)	3 (23)	
	N2	6 (60)	7 (54)	
	N3	1 (10)	2 (15)	
	Metastasis			1.000
	M0	10 (100)	12 (92)	
	M1	0 (0)	1 (8)	
Staging, n (%)				1.000
	III	3 (30)	4 (31)	
	IV	7 (70)	9 (69)	
CCRT, n (%)				0.618
	Adjuvant CCRT	3 (30)	2 (15)	
	Definitive CCRT	7 (70)	11 (85)	
Smoking, n (%)		8 (80)	9 (70)	0.660
Alcohol, n (%)		9 (90)	7 (54)	0.089
Betel nut, n (%)		2 (20)	1 (8)	0.560
Feeding tube prophylaxis, n (%)		8 (80)	13 (100)	0.178

Table 1: Baseline characteristics

3.3 Treatment delivery and compliance

Treatment delivery and compliance of treatment are shown in Table 2. There was no difference in the mean total dose of RT between the two groups, which included 69.79 Gy for the curcumin MW group and 70 Gy for the NSS MW group (p = 0.254). The primary type of RT was three-dimensional (3D) conformal radiation therapy. There were eight patients (80%) in the curcumin MW group and seven patients (54%) in the NSS MW group that completed 3 cycles of cisplatin. The average dose of cisplatin was 215 mg/m^2 in both groups. One patient (10%) in the curcumin MW group and three patients (23%) in the NSS MW group changed concurrent chemotherapy to carboplatin. The mean compliance for the use of mouthwash was 89% in the curcumin MW group and 90% in the NSS MW group.

Variables		Curcumin MW	P value	P-value
Total dose of RT (Gy)				0.254
		69.79±0.63	70±0	
Type of RT, n (%)				1.000
	3D CRT	10 (100)	12 (92)	
	IMRT	0 (0)	1 (8)	
Total cycles of cisplatin				0.569
	3 cycles, n (%)	8 (80)	7 (54)	
	Average dose (mg/m²)	215	215	
	2 cycles, n (%)	1 (10)	4 (31)	
	Average dose (mg/m²)	160	140	
	1 cycle, n (%)	1 (10)	2 (15)	
	Average dose (mg/m²)	80	80	
Change regimen to carboplatin, n (%)		1 (10)	3 (23)	0.604
Mean compliance (%)		89±6.42	90±8.42	0.493

Table 2: Treatment delivery and compliance

4. Outcomes

4.1 Safety and Tolerability

All 23 patients were included in the safety analysis. No side effects, for example, gastric irritation, stomach upset, nausea, or vomiting, were reported from the use of curcumin MW. The toxicities are shown in Table 3.

Toxicities		Curcumin MW (N = 10)	NSS MW (N = 13)	P-value
Oral candidiasis, n (%)		2 (20)	7 (54)	0.99
AKI grade 3, n (%)		5 (50)	4 (31)	0.39
Neutropenia, n (%)				0.33
	Grade 1	2 (20)	0 (0)	
	Grade 2	0 (0)	0 (0)	
	Grade 3	0 (0)	1 (8)	
	Grade 4	0 (0)	1 (8)	

Table 2: Treatment delivery and compliance

Oral candidiasis occurred in the curcumin MW group (20%) and in the NSS MW group (54%). Grade 3 acute kidney injury occurred in the curcumin MW group (50%) and in the NSS MW group (31%). Twenty percent in the curcumin MW group had grade 1 neutropenia, whereas 8% of the patients in the NSS MW group had grade 3 and 4. No liver toxicity was reported in either group. There was no treatment break in the study. The mean compliance for the use of mouthwash was 89% in the curcumin MW group and 90% in the NSS MW group.

Comparing the mean of the pain score (grading by the Numerical Rating Scale), the mean was reduced in the curcumin MW group compared with the NSS MW group at week 2, 4, 7, and 10. However, it was not statistically different between the groups using the curcumin MW and the NSS MW (*P-value* = 0.163) as shown in Figure 3.

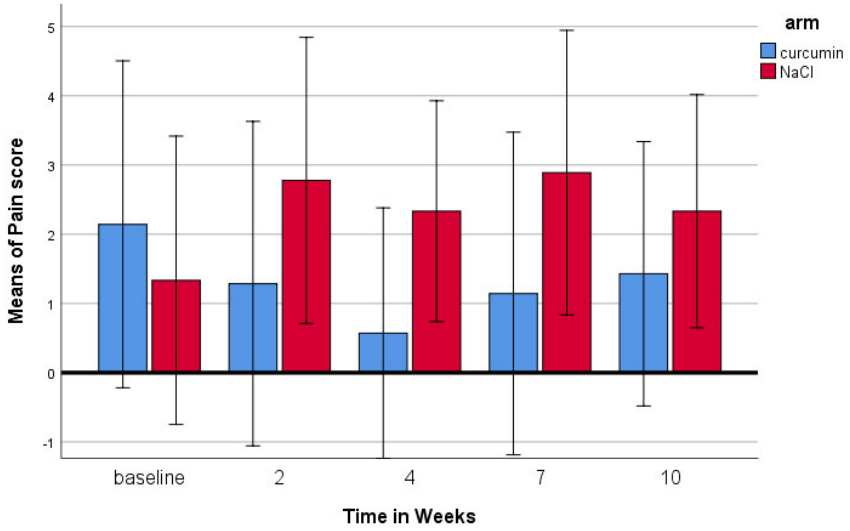

Figure 3: Mean of pain score

4.2 Incidence of Oral Mucositis

Comparing the grade of oral mucositis using the WHO grading scale revealed that in the beginning week, the curcumin MW group exhibited the highest (70%) in grade 0 compared with 84.6% in the NSS MW group. In the second week, the curcumin MW group had the highest (60%) in grade 0, which was the same (61.5%) as the NSS MW group. At week 4, the curcumin MW had the highest (50%) in grade 0, whereas the NSS MW group had 58.3% in grade 3. In week 7, the curcumin MW group had 44.4% in grade 0, whereas the NSS MW group had 58.3% of the samples in grade 3. Finally, in week 10, the curcumin MW had 57.1% of the samples in grade 0, whereas the NSS MW group had 27.3% in grades 0, 2, and 3, as shown in Table 4.

Time	Curcumin group n (%)					NSS group n (%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Baseline	70	20	0	10	0	84.6	7.7	0	7.7	0
Week 2	60	10	10	20	0	61.5	23.1	0	15.4	0
Week 4	50	0	20	20	10	16.7	16.7	8.3	58.3	0
Week 7	44.4	0	22.2	22.2	11.1	8.3	8.3	16.7	58.3	8.3
Week 10	57.1	0	14.3	28.6	0	27.3	9.1	27.3	27.3	9.1

Table 4: Incidence of oral mucositis in the curcumin MW and NSS MW groups during concurrent chemo-radiation therapy

Comparing the incidence of severe oral mucositis (grade 3–4 defined by the WHO grading scale), the incidence was reduced in the curcumin MW group compared with the NSS MW group. In week 4, the group that used curcumin MW had 30%, whereas the NSS MW group had 58.3%. In week 7, the group using curcumin MW had 33.3%, whereas the NSS MW group had 66.6%. And in week 10, the group that used curcumin MW had 28.6%, whereas the NSS MW group had 36.4%. However, the differences between groups were not statistically different as shown in Table 5.

Time	Curcumin group n (%)		NSS group n (%)		P-value*
	Non severe (Grade 0–2)	Severe (Grade 3–4)	Non severe (Grade 0–2)	Severe (Grade 3–4)	
Baseline	90	10	92.3	7.7	0.846
Week 2	80	20	84.6	15.4	0.772
Week 4	70	30	41.7	58.3	0.712
Week 7	66.6	33.3	33.3	66.6	0.387
Week 10	71.4	28.6	63.7	36.4	0.807
* P-value in severe group (grade 3–4)					

Table 5: Incidence of severe oral mucositis in the curcumin MW and NSS MW groups

Figure 4 shows the incidence of oral mucositis defined by the WHO oral mucositis grading scale. The curcumin MW and NSS MW groups showed a trend of increasing incidence at week 2, 4, and 7, but a decrease at week 10. Overall, oral mucositis incidence was reduced in the curcumin MW group compared with the NSS MW group; however, the difference was not statistically significant (p = 0.717).

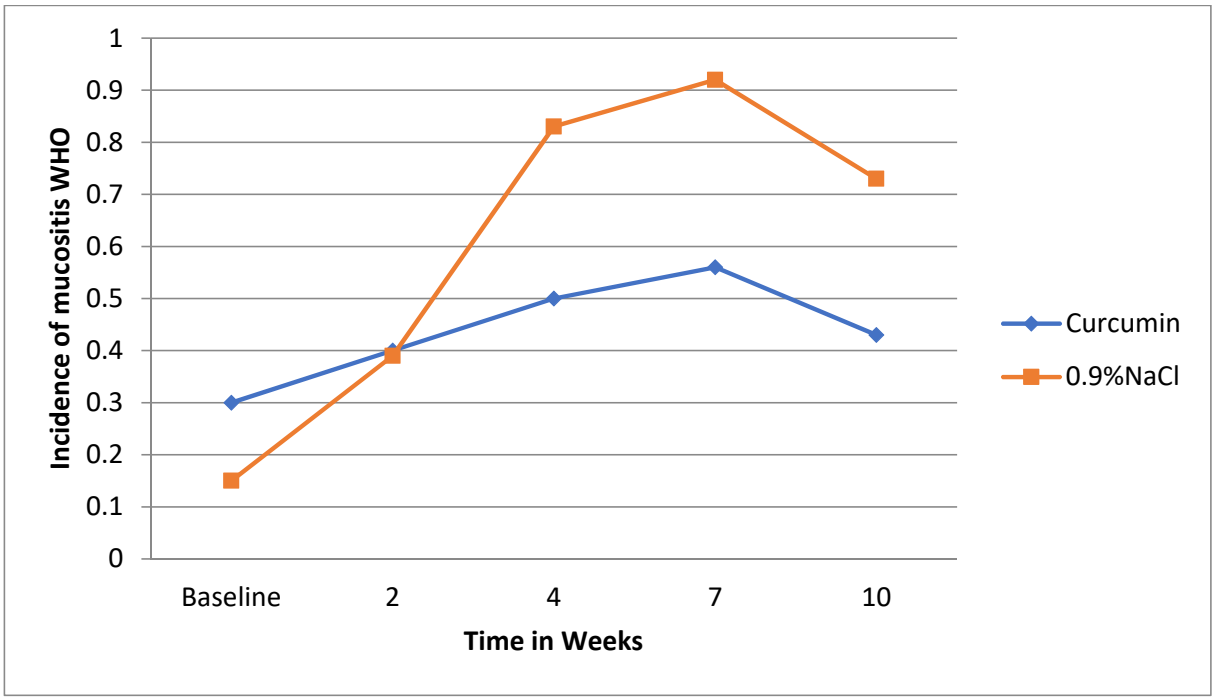

Figure 4: Incidence of oral mucositis through the treatment period

4.3 Severity of Oral Mucositis

The severity of oral mucositis was reduced in patients using curcumin MW compared with NSS MW at weeks 4, 7, and 10, as defined by both the WHO oral mucositis grading scale and the New scoring system for the assessment of clinical trial research. However, only week 4 showed a statistical difference as determined by the New scoring system for the assessment of clinical trial research, in which the curcumin MW group had a mean of 0.09. In contrast, the NSS MW group had a mean score of 0.32 ($p = 0.016$) (Table 6).

Variable	Baseline (week1)			Week2			Week4			Week7			Week10		
	Mean	S.D.	P value	Mean	S.D.	P value	Mean	S.D.	P value	Mean	S.D.	P value	Mean	S.D.	P value
Mucositis New score															
Curcumin	0.07	0.15	0.223	0.11	0.17	0.910	0.09	0.15	0.016	0.27	0.44	0.426	0.11	0.24	0.687
0.9%NaCl	0.01	0.02		0.11	0.12		0.32	0.21		0.44	0.49		0.15	0.14	
Mucositis WHO score															
Curcumin	0.50	0.97	0.619	0.90	1.29	0.682	1.40	1.58	0.268	1.56	1.59	0.122	1.14	1.46	0.342
0.9%NaCl	0.31	0.86		0.69	1.11		2.08	1.24		2.50	1.09		1.82	1.40	

Table 6: Mean severity of oral mucositis

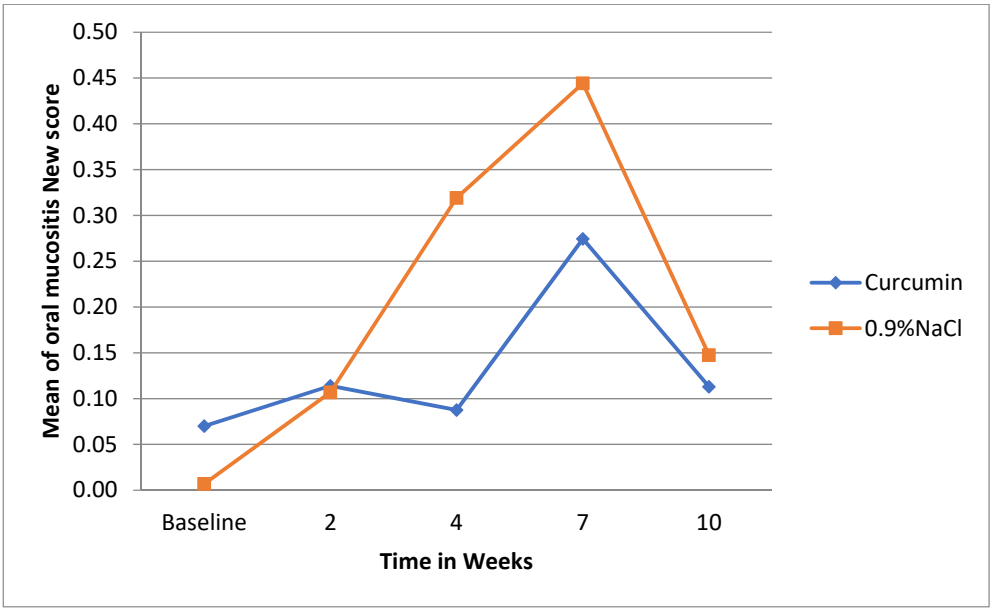

Figure 5: Mean severity of oral mucositis by the New score system

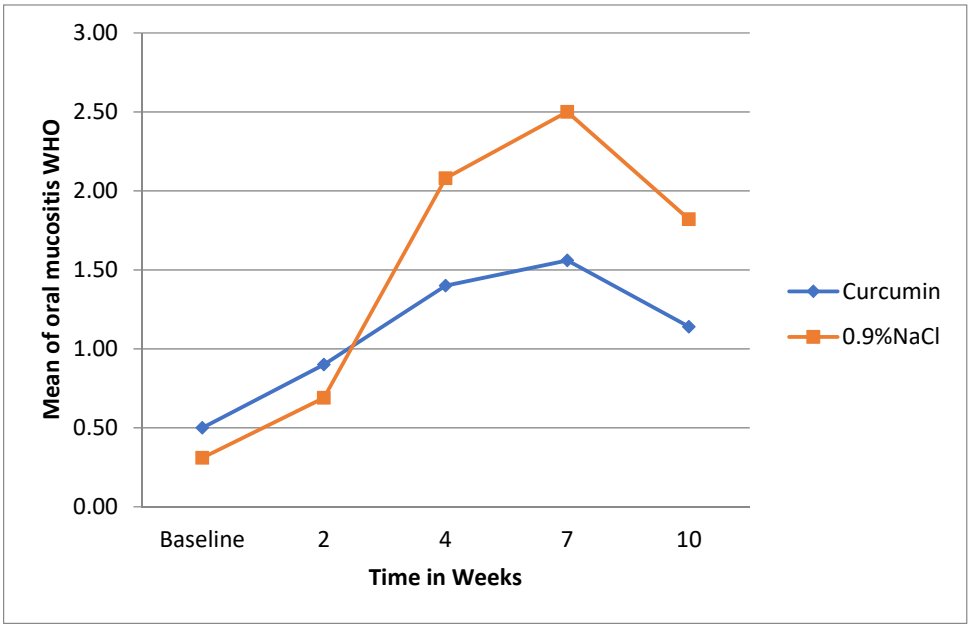

Figure 6: Mean severity of oral mucositis by the WHO grading scale

5. Discussion

Oral mucositis is a common and severe complication in patients receiving CCRT for head and neck cancer. Severe oral mucositis can also impede optimal anticancer therapy delivery, thus requiring dose reduction or treatment interruption. These disruptions in dosing can negatively impact patient outcome and survival [1]. Therefore, oral mucositis control is essential and indispensable for prognosis and improves patient quality of life. A wide variety of agents have been tested to prevent or treat oral mucositis; however, the use of natural-based compounds has increased in interest recently because of reduced side effects compared with chemical drugs.

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a polyphenolic compound and the primary yellow pigment extracted from the rhizome of turmeric (Curcuma longa), which belongs to the ginger family, Zingeberaceae. Curcumin occurs in the pharmacopeias as an antiseptic, analgesic, anti-inflammatory, and wound healing agent. Scientific studies have validated these ethnomedicinal properties [25]. Studies indicate that Curcuminoids, which include mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin, are the active components and these phytochemicals like turmeric also possess antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, antimutagenic, immunomodulatory, and wound

healing effects [26-28].

Aggarwal et al. reported that curcumin has the potential to inhibit NF-κB. The expression of several genes regulated by NF-κB is suppressed by curcumin [29]. These include cell surface adhesion molecules, chemokines, TNF, MMP9, COX2, and NOS. Because these genes are important regulators of inflammation, the suppression of these genes may explain the anti-inflammatory effects of curcumin. Land et al. performed a study on the role of curcumin and the inhibition of NF-κB in the onset of methotrexate-induced mucosal barrier injury in the intestinal mucosa of rats. They concluded that inhibition of NF-κB increases intestinal side effects of the anticancer treatment, suggesting a safe use of curcumin and caffeic acid phenethyl ester (CAPE) in combination with anticancer treatment [15].

Many studies have demonstrated the role of curcumin as an anti-oxidant, anti-inflammatory, anti-microbial, and anti-carcinogenic agent with multifaceted therapeutic activities, which suggest possible benefits for treating oral mucositis. Elad et al. performed a pilot study on seven pediatric patients receiving chemotherapy to evaluate the efficacy of curcumin oil in controlling oral mucositis signs and symptoms. They concluded that curcumin mouthwash is well tolerated and efficacious [30]. In addition, Patil et al. reported that mouthwash containing 0.4% curcumin is safe and effective in controlling oral mucositis signs and symptoms in 10 cancer patients receiving radiotherapy and chemotherapy [13].

Rao et al. evaluated the efficacy of curcumin on radiation-induced mucositis. They concluded that gargling with curcumin significantly benefited head and neck cancer patients by delaying and reducing the severity of oral mucositis [31]. Mansourian et al. reported that a topical gel containing Curcuma longa's derivate could effectively reduce oral mucositis symptoms in patients undergoing head and neck cancer radiotherapy [32]. Recently, Shah et al. have demonstrated the effectiveness of 0.1% curcumin mouthwash in delay the onset of radiation-induced oral mucositis [14].

Our study was an investigator-blinded, pilot randomized controlled trial evaluating the safety and efficacy of curcumin mouthwash to prevent severe oral mucositis in patients with head and neck cancer receiving CCRT and high-dose cisplatin. There were no differences in the baseline characteristics between the two groups, except more patients in the NSS MW group had primary nasopharynx cancer, which is considered to affect the area of radiation field and type of RT. However, we found no difference in the type of RT between the two groups over the entire treatment course.

This pilot results showed the feasibility and acceptability of curcumin MW in patients with head and neck cancer receiving CCRT and high-dose cisplatin. There were no side effects or safety concerns. The curcumin MW tended to reduce the incidence of severe oral mucositis from week four until the end of treatment. However, we could not demonstrate the superiority of curcumin MW in reducing the incidence of severe oral mucositis as we anticipated. This may be explained by the fact that our small sample size limits our ability to detect significant differences between groups and most RT types in our study received three-dimensional (3D) conformal radiation therapy (100% in curcumin MW group and 92% in NSS MW group). Thus, it is unclear whether it affects severe oral mucositis incidence compared with intensity-modulated radiotherapy (IMRT). As previously reported by Ghosh et al., the 3D-CRT group had significantly more oral mucositis than the IMRT group [33]. *The severity of oral mucositis was reduced in the curcumin MW group over the treatment period with statistically significance at week 4 using the New score system (0.09 vs. 0.32; $p = 0.016$).* These data indicate that curcumin mouthwash has the potential to prevent severe oral mucositis in patients receiving CCRT.

To our knowledge, this is the first pilot study evaluating the feasibility, acceptability, and efficacy of curcumin MW in coconut oil solvent for the prevention of severe oral mucositis in patients with head and neck cancer receiving CCRT and high-dose cisplatin. Several clinical studies have previously assessed the efficacy of curcumin as a topical agent in preventing and treating oral mucositis. Thus, our data provide evidence that curcumin in mouthwash form is a readily available, safe, and potentially effective agent to prevent severe oral mucositis.

There were several limitations to our study. First, the small sample size suggests that further studies should be performed with more patients to establish the role of curcumin mouthwash in managing CCRT-induced oral mucositis. Secondly, the manufacturing process for mouthwash relies on coconut oil as a solvent. Coconut oil may itself affect the study results. Third, our trial did not adjust for balancing factors in the analysis, such as the type of primary cancer, or type and dose of radiation. This could potentially result in differences. Finally, our study was a single investigator-blinded design; hence, we could not manufacture the placebo that tastes and is colored like the curcumin mouthwash.

6. Conclusion

The results of this pilot study suggest the feasibility and acceptability of curcumin mouthwash in locally advanced head and neck cancer patients undergoing CCRT. A large-scale randomized controlled trial is feasible and should be encouraged.

Conflict of Interest

The authors declare that they have no potential conflicts of interest.

References

1. Naidu, M. U. R., Ramana, G. V., Rani, P. U., Suman, A., & Roy, P. (2004). Chemotherapy-induced and/or radiation therapy-induced oral mucositis-complicating the treatment of cancer. Neoplasia, 6(5), 423-431.
2. Elad, S., Yarom, N., Zadik, Y., Kuten-Shorrer, M., & Sonis, S. T. (2022). The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. CA: a

cancer journal for clinicians, 72(1), 57-77.
3. Elting, L. S., Keefe, D. M., Sonis, S. T., Garden, A. S., Spijkervet, F. K. L., Barasch, A., ... & Burden of Illness Head and Neck Writing Committee. (2008). Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. Cancer, 113(10), 2704-2713.
4. Anderson, C. M., Lee, C. M., Saunders, D. P., Curtis, A., Dunlap, N., Nangia, C., ... & Buatti, J. M. (2019). Phase IIb, randomized, double-blind trial of GC4419 versus placebo to reduce severe oral mucositis due to concurrent radiotherapy and cisplatin for head and neck cancer. Journal of Clinical Oncology, 37(34), 3256.
5. Moslemi, D., Nokhandani, A. M., Otaghsaraei, M. T., Moghadamnia, Y., Kazemi, S., & Moghadamnia, A. A. (2016). Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature. Radiotherapy and Oncology, 120(1), 13-20.
6. Delavarian, Z., Pakfetrat, A., Ghazi, A., Jaafari, M. R., Homaei Shandiz, F., Dalirsani, Z., ... & Rahimi, H. R. (2019). Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers. Special Care in Dentistry, 39(2), 166-172.
7. Brown, T. J., & Gupta, A. (2020). Management of cancer therapy–associated oral mucositis. JCO oncology practice, 16(3), 103-109.
8. Epstein, J. B., Silverman Jr, S., Paggiarino, D. A., Crockett, S., Schubert, M. M., Senzer, N. N., ... & Leveque, F. G. (2001). Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: Results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer, 92(4), 875-885.
9. Oronsky, B., Goyal, S., Kim, M. M., Cabrales, P., Lybeck, M., Caroen, S., ... & Oronsky, A. (2018). A review of clinical radioprotection and chemoprotection for oral mucositis. Translational oncology, 11(3), 771-778.
10. Chaturvedi, T. P. (2009). Uses of turmeric in dentistry: An update. Indian Journal of Dental Research, 20(1), 107.
11. Nagpal, M., & Sood, S. (2013). Role of curcumin in systemic and oral health: An overview. Journal of natural science, biology, and medicine, 4(1), 3.
12. Mimeault, M., & Batra, S. K. (2011). Potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy. Chinese medicine, 6(1), 1-19.
13. Patil, K., Guledgud, M. V., Kulkarni, P. K., KeShari, D., & Tayal, S. (2015). Use of curcumin mouthrinse in radio-chemotherapy induced oral mucositis patients: a pilot study. Journal of clinical and diagnostic research: JCDR, 9(8), ZC59.
14. Shah, S., Rath, H., Sharma, G., Senapati, S. N., & Mishra, E. (2020). Effectiveness of curcumin mouthwash on radiation-induced oral mucositis among head and neck cancer patients: A triple-blind, pilot randomised controlled trial. Indian Journal of Dental Research, 31(5), 718.
15. Van't Land, B., Blijlevens, N. M. A., Marteijn, J., Timal, S., Donnelly, J. P., de Witte, T. J. M., & M'rabet, L. (2004). Role of curcumin and the inhibition of NF-κB in the onset of chemotherapy-induced mucosal barrier injury. Leukemia, 18(2), 276-284.
16. Pawar, H. A., Gavasane, A. J., & Choudhary, P. D. (2018). A novel and simple approach for extraction and isolation of curcuminoids from turmeric rhizomes. Nat. Prod. Chem. Res, 6(1).
17. Sobankumar, D. R., Rajan, A., Christudhas, J., & GnanaRaj, A. (2018). Process for the extraction and encapsulation of curcumin in nanoemulsion using edible oils. International Journal of Advanced Scientific Research and Management, 3(7), 11-15.
18. Takenaka, M., Ohkubo, T., Okadome, H., Sotome, I., Itoh, T., & Isobe, S. (2013). Effective extraction of curcuminoids by grinding turmeric (Curcuma longa) with medium-chain triacylglycerols. Food Science and Technology Research, 19(4), 655-659.
19. Olsen, S. J., & Frank-Stromborg, M. Instruments for clinical health-care research. Jones & Bartlett Learning.
20. Sonis, S. T., Eilers, J. P., Epstein, J. B., LeVeque, F. G., Liggett Jr, W. H., Mulagha, M. T., ... & Mucositis Study Group. (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Cancer, 85(10), 2103-2113.
21. McGuire, D. B., Yeager, K. A., Dudley, W. N., Peterson, D. E., Owen, D. C., Lin, L. S., & Wingard, J. R. (1998). Acute oral pain and mucositis in bone marrow transplant and leukemia patients: data from a pilot study. Cancer nursing, 21(6), 385-393.
22. Cella, D., Pulliam, J., Fuchs, H., Miller, C., Hurd, D., Wingard, J. R., ... & Giles, F. (2003). Evaluation of pain associated with oral mucositis during the acute period after administration of high-dose chemotherapy. Cancer, 98(2), 406-412.
23. U.S. Department of Heath and Human services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. National Cancer Institute; 2017.
24. The R Project for Statistical Computing [Internet]. In R-project.org; 2019.
25. Perkins, S., Verschoyle, R. D., Hill, K., Parveen, I., Threadgill, M. D., Sharma, R. A., ... & Gescher, A. J. (2002). Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiology Biomarkers & Prevention, 11(6), 535-540.
26. Chattopadhyay, I., Biswas, K., Bandyopadhyay, U., & Banerjee, R. K. (2004). Turmeric and curcumin: Biological actions and medicinal applications. Current science, 44-53.
27. Chainani-Wu, N. (2003). Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). The Journal of Alternative & Complementary Medicine, 9(1), 161-168.

28. Calabrese, V., Bates, T. E., Mancuso, C., Cornelius, C., Ventimiglia, B., Cambria, M. T., ... & Dinkova-Kostova, A. T. (2008). Curcumin and the cellular stress response in free radical-related diseases. Molecular nutrition & food research, 52(9), 1062-1073.
29. Silverman Jr, S. (2007). Diagnosis and management of oral mucositis. The journal of supportive oncology, 5(2 Suppl 1), 13-21.
30. Elad, S., Meidan, I., Sellam, G., Simaan, S., Zeevi, I., Waldman, E., ... & Revel-Vilk, S. (2013). Topical curcumin for the prevention of oral. Health Med, 19(3), 21-24.
31. Rao, S., Dinkar, C., Vaishnav, L. K., Rao, P., Rai, M. P., Fayad, R., & Baliga, M. S. (2014). The Indian spice turmeric delays and mitigates radiation-induced oral mucositis in patients undergoing treatment for head and neck cancer: an investigational study. Integrative cancer therapies, 13(3), 201-210.
32. Mansourian, A., Amanlou, M., SHIRAZIAN, S., MOOSAVIAN, J. Z., & Amirian, A. (2015). The effect of "Curcuma Longa" topical gel on radiation-induced oral mucositis in patients with head and neck cancer. Int J Radiat Res, 13(2):269–74.
33. Ghosh, G., Tallari, R., & Malviya, A. (2016). Toxicity profile of IMRT vs. 3D-CRT in head and neck cancer: A retrospective study. Journal of clinical and diagnostic research: JCDR, 10(9), XC01.