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Phytochemical-rich vegetable and fruit juice alleviates oral mucositis during concurrent chemoradiotherapy in patients with locally advanced head and neck cancer

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ABSTRACT

Background: Concurrent chemoradiotherapy (CCRT)-induced oral mucositis (OM) causes oral pain, malnutrition, and impaired quality of life in patients with head and neck cancer (HNC). Phytochemicals play a potential role in eliminating cancer therapy toxicity.
Objective: To evaluate the effect of phytochemical-rich vegetable and fruit juice (VFJ) consumption in preventing CCRT-induced OM among patients with locally advanced HNC.
Methods: Forty-nine patients with HNC undergoing CCRT were enrolled. All patients received nutritional counseling before CCRT and weekly follow-up. The VFJ group (25 patients) received 600 mL/day VFJ, 5 days/week for two weeks preceding CCRT and during CCRT, and the control group (24 patients) did not. The contents of total polyphenols and carotenoids in the VFJ were determined. Changes in anthropometric, dietary, and laboratory profiles were compared. Assessment of OM was based on the World Health Organization (WHO) scoring system.
Results: Total polyphenols content was 64.6 mg gallic acid equivalents per 100 mL of the VFJ, and the main carotenoids were β-carotene and lycopene. The mean daily consumption of the VFJ was 538 mL for VFJ group. Changes in body weight, albumin, and energy intake were not significantly different between the two groups. The incidence of ulcerative OM was significantly lower in VFJ (64.0%) than in control (95.8%) subjects at week 6 of CCRT. Multiple logistic regressions revealed that VFJ consumption correlated significantly with lower risks of ulcerative OM.
Conclusion: Consumption of VFJ rich in phytochemicals including total polyphenols and carotenoids effectively alleviates the severity of CCRT-induced OM among patients with locally advanced HNC.
Section: Preventive Medicine; Dietary Therapy/Nutrition Supplements
Taxonomy: (classification by EVISE)Preventive medicine, dietary therapy, nutrition supplements.

Abbreviations: COX-2, cyclooxygenase-2; IL, interleukin; iNOS, inducible nitric oxide synthases; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; RNS, reactive nitrigen species; TNF-α, tumor necrosis factor-α.

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List of abbreviations

Alb	albumin
BMI	body mass index
BUN	blood urea nitrogen
CCRT	concurrent chemoradiotherapy
CREA	creatinine
CT	chemotherapy
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck 35
GAE	gallic acid equivalent
Gy	gray
Hgb	hemoglobin
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinomas
hs-CRP	high-sensitivity C-reactive protein
OM	oral mucositis
RT	radiotherapy
TAF	Taiwan Accreditation Foundation
TC	total cholesterol
TLC	total lymphocyte count
TNM	tumor-node-metastasis
VFJ	vegetable and fruit juice
WBC	white blood cell
WHO	World Health Organization

1. Introduction

More than 90% of head and neck cancers (HNCs) are squamous cell carcinomas (HNSCC) found in the oral, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx, paranasal sinus, nasal cavity, and salivary glands regions.[1] HNC is the seventh most common cancer in the world according to the Global Cancer Observatory estimates from the International Agency for Research on Cancer, with approximately 930,000 new cases and 460,000 deaths in 2020.[2] In Taiwan, HNC is ranked as the sixth most common cancer and the sixth leading cause of cancer death,[3] with oral cancer having one of the highest incidences worldwide.[4]

Concurrent chemoradiotherapy (CCRT) is the standard therapeutic approach for locally advanced HNC.[5] After initiating chemotherapy (CT), radiotherapy (RT), or a combination of both, mucositis generally occurs within 3–10 days in the labial and buccal mucosa, tongue, floor of the mouth, and soft palate.[6] Moreover, up to 85% of the patients undergoing CCRT develop severe oral mucositis (OM),[7] the presence of which often leads to several nutrition-impacted symptoms, including oral pain and dysphagia. This can further contribute to reduced food intake, weight loss, dehydration, augmented inflammation, and treatment interruption.[8] Radiation therapy may also damage salivary glands and cause dry mouth (xerostomia), which is one of the contributors to oral mucositis.[9] Oral mucositis is a typical side effect of iatrogenic toxicity, and current therapies against CCRT-induced mucositis have shown very limited efficacy in patients with HNC.[10]

CCRT-induced OM may be due to the generation of reactive oxygen species (ROS) that increase oxidative stress and subsequently induce the release of inflammatory cytokines (tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β and IL-6). Oxidative stress has thus been suggested as one of the major causative factors of OM.[11] A systematic review also indicated that several natural agents containing phytochemicals, such as polyphenols, carotenoids, triterpenes, and essential oils, which exert antioxidant, anti-inflammatory, and antimicrobial properties, are effective alternatives to synergistic therapy for OM lesions after RT, CT, or both.[12]

Vegetables and fruits contain large amounts of phytochemicals.[13] Phytochemicals, such as polyphenols and carotenoids, contribute to the antioxidant and anti-inflammatory properties in plant foods and can stimulate DNA repair.[14] In human studies, the consumption of vegetables, fruits, or beverages containing ample polyphenols can increase the body's antioxidant capacity within a few hours.[15,16] A clinical trial assessing the effects of the direct contact of polyphenols in mouthwash demonstrated the prevention and reduction of the severity of oral mucosal ulcers caused by RT in patients with HNC.[17]

To our knowledge, there have been no studies exploring the effects of a natural plant-based food regimen enriched in phytochemicals in terms of reducing the severity of OM during CCRT among patients with HNC. In this investigation, we aimed to explore whether vegetable and fruit juice (VFJ) consumption, at 600 mL/day for 5 days per week, is effective in minimizing CCRT-induced OM in patients with locally advanced HNC compared to the control group. The impact of VFJ consumption on the intensity of oral pain and dry mouth, nutritional status, and inflammation parameters was also evaluated.

2. Materials and methods

2.1. Study participants

We recruited 49 patients who were newly diagnosed with stage III and IV HNC, classified using the seventh edition tumor-node-metastasis (TNM) cancer staging system of the American Joint Committee on Cancer and the International Union for Cancer Control.[18] The patients were within the age range of 20–65 years, and their Eastern Cooperative Oncology Group performance status scale scores were between 0 and 2.[19] Patients were recruited from the Oncology or Otolaryngology (ENT) ward and clinic of the National Taiwan University Hospital between October 2013 and October 2014. The exclusion criteria included (i) poor control of chronic diseases such as diabetes, cardiovascular diseases, chronic kidney diseases, severe infection, and OM, and (ii) an allergy to certain fruits or vegetables. The Research Ethics Committee approved the study protocol (NTUH-REC No.:201307076RINB). All subjects completed the informed consent process and signed consent forms before participation.

2.2. Chemoradiotherapy administration and ethical considerations

All subjects underwent conventional fractioned radiation (2 Gy/day, 5 days/week) with concurrent chemotherapy. Arc-controlled radiotherapy, intensity-modulated radiotherapy, or image-guided spiral knife therapy was prescribed to treat the patients, with the total radiation dose range being 60–70 Gy. Concurrent chemotherapy was administered in all patients who received cisplatin (CDDP, 40 mg/m^2 intravenous infusion weekly, six times during RT), except for one patient in the experimental group who received arterial chemotherapy (cisplatin, CDDP 100 mg/m^2 intra-arterial infusion triweekly, three times during RT). Patients who received neoadjuvant chemotherapy were treated with European docetaxel (Taxotere), cisplatin, 5-fluorouracil, epirubicin, and mitomycin.

2.3. Nutritional interventions and dietary assessments

We employed a prospective, quasi-experimental design, and purposive sampling was applied to assign participants to the VFJ supplementation group (VFJ group) or the control group. In this study, we first recruited patients for the VFJ group, followed by the control group. The VFJ and control subjects received usual care from the medical team and were provided nutrition counseling by a registered dietician before the beginning of CCRT and during treatment. Patients in the VFJ group received additional 600 mL VFJ (300 mL/cup, two cups/day). The control patients did not receive specific juices as placebos. The dietician also contacted all participants weekly via telephone to offer advice on nutrition-related problems and tracked the compliance of VFJ consumption. The 24-h dietary recall method was used by the dietician to assess nutrient and food intake for both groups at baseline and week 6 of CCRT.

2.4. Preparation and analysis of total polyphenols and carotenoids for the VFJ group

In this study, we used 12 types of vegetables and fruits including carrot (*Daucus carota* subsp. *sativus*), beetroot (*Beta vulgaris* var. *rubra*), celery (*Apium graveolens*), cucumber (*Cucumis sativus*), alfalfa sprouts (*Medicago sativa*), tomato (*Solanum lycopersicum*), apple (*Malus domestica*), guava (*Psidium guajava*), pineapple (*Ananas comosus*), orange (*Citrus X sinensis*), lemon (*Citrus limon*), and Chinese wolfberry (*Lycium barbarum*), commonly found in daily diets or food markets in Taiwan. All vegetable and fruit materials were purchased based on an in-hospital standardized procurement process that would uniform growth stages, maturations, sizes, and product qualities; they were mostly grown domestically and provided by New Taipei City Fruit and Vegetable Marketing Co., Ltd. Parts of the vegetables and fruits contained in our VFJ included non-edible peels, seeds, and young leaves. Various vegetables and fruits (raw weight) were used, and ice water was added to blend 600 mL of juice. The vegetables and fruits used to blend the VFJ are listed in Table 1a. A 600-mL vegetable and fruit juice were composed of two servings each of vegetable and fruit. All VFJ preparations were freshly made using a high-performance blender (Vitamix, Vita-Mix Corporation, OH, United States) based on a standardized recipe by well-trained chef members of the Department of Dietetics and Nutrition of the Taipei City Hospital (Taipei, Taiwan). Juices (600 mL/day, 5 days/week) were directly delivered to the homes of the VFJ group members for consumption two weeks before CCRT initiation. Moreover, the refrigerated juices were sent to the hospital and were delivered by an oncology nurse practitioner to each patient for drinking while the patient was receiving CCRT. The total polyphenol and carotenoid contents of the VFJ were determined by a laboratory (Super Laboratory, New Taipei City, Taiwan) accredited by the Taiwan Accreditation Foundation (TAF). Total polyphenol analysis was performed spectrophotometrically using the Folin-Ciocalteu method and gallic acid as a reference compound.[20] Analyses of β-carotene and lycopene, lutein, and zeaxanthin were performed using high-performance liquid chromatography and the spectrophotometric method, respectively.[21,22] As shown in Table 1b, the total polyphenols content was 64.6 ± 2.1 mg gallic acid equivalent (GAE) per 100 mL of the VFJ. The main carotenoids were β-carotene (10.3 ± 0.3 mg/100 mL) and lycopene (29.3 ± 0.3 mg/100 mL), followed by zeaxanthin (3.7 ± 0.1 mg/100 mL) and lutein (0.1 ± 0.0 mg/100 mL).

2.5. Assessment of oral mucositis, oral pain, and dry mouth

We employed the World Health Organization (WHO) oral Toxicity Scale to assess the OM severity.[23] The WHO scoring system is dependent on both objective and subjective variables and measures the anatomical, symptomatic, and functional components of OM. The WHO scoring system grades for OM are defined as follows: grade 0 (none), no mucositis; grade 1 (mild), oral soreness, erythema; grade 2 (moderate), erythema, ulcers, solid diet tolerated; grade 3 (severe), oral ulcers, liquid diet only; and grade 4 (life-

Table 1
Ingredients and phytochemical contents of the vegetable and fruit juice.

(a) Vegetables and fruits used to blend the vegetable and fruit juice (VFJ)

Vegetables and fruits	Characteristics	g (raw weight)/600 mL[a]
Vegetables		
Carrot (*Daucus carota* subsp. *sativus*)	with skin	40
Beetroot (*Beta vulgaris* var. *rubra*)	Peeled	24
Celery *(Apium graveolens)*	with some tender leaves	40
Cucumber (*Cucumis sativus*)	with skin	40
Alfalfa sprouts (*Medicago sativa*)	–	6
Tomato (*Solanum lycopersicum*)	–	40
Fruits		
Apple (*Malus domestica*)	with peel	50
Guava (*Psidium guajava*)	with seeds	40
Pineapple (*Ananas comosus*)	peeled	50
Orange (*Citrus X sinensis*)	peeled, with seeds	50
Lemon (*Citrus limon*)	peeled, with seeds	6
Chinese wolfberry (*Lycium barbarum*)	dried fruit	4

(b) Total polyphenol and carotenoid contents of the vegetable and fruit juice (VFJ)

Phytochemicals	mg/100 mL	mg/600 mL
Total polyphenols	64.6 ± 2.1	387.6 ± 12.9
Carotenoids		
β-carotene	10.3 ± 0.3	61.7 ± 2.0
Lycopene	29.3 ± 0.3	175.8 ± 2.0
Zeaxanthin	3.7 ± 0.1	22.3 ± 0.4
Lutein	0.1 ± 0.0	0.3 ± 0.0

Concentrations of phytochemicals were expressed as mean ± standard deviations (SD) of three replicates. The total polyphenols content was expressed as mg of gallic acid equivalents per 100 and 600 mL of the vegetable and fruit juice. Abbreviations: VFJ, vegetable and fruit juice.

[a] A 600-mL vegetable and fruit juice was composed of two servings of vegetable and two servings of fruit. Abbreviations: VFJ, vegetable and fruit juice.

threatening), oral feeding is impossible and requires parenteral nutrition. The same oncology nurse practitioner performed the mucositis assessment at baseline, week 3 and week 6 of CCRT.

Oral pain and dry mouth were assessed based on the European Organization for Research and Treatment of Cancer (EORTC) head and neck cancer module (QLQ-H&N35).[24] Composite scores were created utilizing specific questions from the EORTC QLQ-H&N35. Items 1–4 were used to evaluate oral pain and item 11 to evaluate dry mouth. Items were scored based on four-point Likert-type categorical scales (1: not at all, 2: a little, 3: quite a bit, 4: very much). The subsets of these scores were evaluated at baseline and week 6 of CCRT. Reported intensities of oral pain and dry mouth were based on the patient's subjective symptoms during the previous week.

2.6. Measurement of anthropometric and laboratory parameters

Body weight, body mass index (BMI), and body weight loss were measured at baseline and week 6 of CCRT. Ten milliliter of venous blood after overnight fasting for at least 8 h was collected for biochemical analysis. All specimens were stored at 2–8 °C and were sent to a TAF-certified laboratory (Yea-Dong Institute of Medical Laboratory, New Taipei City, Taiwan). White blood cell (WBC) count, percentage of lymphocytes, and hemoglobin (Hgb) were analyzed using an automated hematology analyzer, and the total lymphocyte count (TLC) was obtained by multiplying the percentage of lymphocytes by the total WBC count. Albumin (Alb), total cholesterol (TC), blood urea nitrogen (BUN), creatinine (CREA), and high-sensitivity C-reactive protein (hs-CRP) levels were analyzed using an auto-analyzer (Beckman Coulter Automated Chemistry Analyzer AU680, CA, United States).

2.7. Statistical analysis

The sample size of the study was estimated based on the minimum detectable difference in means (i.e., MNA = 17, expected standard deviation of residuals = 3.6, 1-b = 0.8, a = 0.05), so the minimum sample size calculated for each group was 24. Descriptive statistics were used to analyze demographic, clinical, dietary intake, and all other outcome variables. Differences between the two groups at baseline and at week 6 of CCRT were determined using independent *t*-test or Mann–Whitney *U* test for continuous variables and the chi-squared test for categorical variables (all log-transformed, except for age). Fisher's exact test was performed if $n < 5$. The paired *t*-test or Wilcoxon signed-rank test was used to determine the differences within each group. The dichotomized mucositis level was categorized as grade 0–1 (non-ulcerative OM) and grade 2–4 (ulcerative OM). Multivariable logistic regression analysis was used to determine the independent association between clinical characteristics, intervention, and severity of mucositis. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Descriptive characteristics of the study population

Forty-nine patients with locally advanced HNC undergoing CCRT were enrolled in this study. The VFJ group (25 patients) received 600 mL/day VFJ, 5 days/week for the two weeks preceding CCRT and during CCRT, and the control group (24 patients) did not. The demographic and clinical characteristics of the patients are presented in Table 2. In terms of the demographic characteristics, the mean age and BMI were similar between the intervention and control groups. For the other demographic characteristics, sex distribution, education level, cigarette smoking, alcohol consumption, and betel nut chewing were not significantly different between the two groups at baseline ($p > 0.05$). Regarding characteristics related to clinical treatment, the proportion of patients with stage IV (IVA, IVB) disease was significantly higher ($p = 0.049$) in the VFJ group (96%) than in the control group (75%). Furthermore, there were no significant differences in the distribution of other clinical indicators, including comorbidities, primary tumor location, cancer stage, radiotherapy type, total radiation dose, and neoadjuvant chemotherapy between the two groups ($p > 0.05$).

3.2. Assessment of anthropometric data, laboratory data, and nutrient intake

The effects of VFJ supplementation on anthropometric, biochemical profiles, and nutrient intake status between the VFJ and control subjects are presented in Table 3. Laboratory measurements including Alb, TC, BUN, and CREA at baseline and week 6 of CCRT, as well as the changes between the two time points were not significantly different ($p > 0.05$). Comparing within-group changes, WBC, TLC, Hgb, body weight, and BMI were significantly lower at week 6 of CCRT than at baseline ($p < 0.05$). Moreover, the hs-CRP levels of both groups were significantly elevated at week 6 of CCRT compared to baseline ($p < 0.05$). Changes in WBC, TLC, Hgb, hs-CRP, body weight, and BMI at week 6 of CCRT were not significantly different between the two treatment groups.

Energy intake was significantly reduced within each group from baseline to week 6 of CCRT ($p < 0.05$). Furthermore, the change in total energy (kcal/day) intake was not significantly different between the two groups (-329 ± 480 vs -489 ± 613, $p = 0.314$). On the other hand, both groups consumed similar amounts of fruit and vegetables (servings/day) from the regular diet at baseline (3.94 ± 1.87 vs 3.60 ± 2.11, $p = 0.558$) and week 6 of CCRT (0.54 ± 1.15 vs 1.17 ± 1.42, $p = 0.098$), whereas the VFJ group had additional VFJ consumption with an average of 588 ± 60 mL/day at baseline and 486 ± 167 mL/day at week 6 of CCRT (an average of 538 ± 62 mL/day during the entire intervention period). Furthermore, 5 (20%) and 6 (25%) patients in the VFJ and control groups, respectively, were prescribed enteral feeding for nutrition supplementation; partial parenteral nutrition was only administered to two patients in the control group (data not shown).

3.3. Clinical factors associated with non-ulcerative and ulcerative oral mucositis

The distributions of grades 0–4 OM between the VFJ and control group at week 3 and week 6 are presented in Fig. 1. The statistically significant differences in the distribution of grades 0–4 OM were observed between the VFJ and control group at week 3 ($p = 0.008$) and week 6 ($p = 0.039$) of CCRT. At week 3, the proportion of grade 2 and grade 3 OM for the VFJ group were only 16% and 8%, respectively, whereas they were as high as 54.2% and 12.5%, respectively, for the control group. At week 6, the distribution of grades 2, 3, and 4 OM in the VFJ group were12%, 40%, 12%, respectively, and those for the control group were 33.3%, 37.5%, and 25.0%, respectively, revealing that more patients in the control group developed ulcerative OM. The distribution of demographic or clinical factors between non-ulcerative (grade 0–1) and ulcerative (grade 2–4) OM among all patients with HNC at week 6 of CCRT are shown in Table 4. Patients with ulcerative OM were 79.6% ($n = 39$), of which 16 (64.9%) were in the VFJ arm and 23 (95.8%) in the control arm. We also observed that hs-CRP levels ≥ 0.1 mg/dL were more commonly observed in ulcerative OM than the non-ulcerative

Table 2
Descriptive characteristics among head and neck patients receiving CCRT at baseline.

Characteristics	VFJ group (n = 25)	Control group (n = 24)	*p*-value
Age (years)	47.6 ± 9.5	51.2 ± 7.5	0.147
Sex, n (%)			>0.999
Male	21 (84.0)	21 (87.5)	
Female	4 (16.0)	3 (12.5)	
Body mass index (kg/m^2)	25.6 ± 4.5	24.6 ± 3.3	0.341
Education, n (%)			0.702
High school or lower	20 (80.0)	21 (87.5)	
College or higher	5 (20.0)	3 (12.5)	
Cigarette smoking status, n (%)	14 (56.0)	18 (75.0)	0.162
Alcohol consumption, n (%)	10 (40.0)	10 (41.7)	0.906
Betel nut chewing, n (%)	10 (40.0)	10 (41.7)	0.906
Comorbidities, n (%)			>0.999
2 conditions	2 (8.0)	2 (8.3)	
1 condition	5 (20.0)	5 (20.8)	
None	18 (72.0)	17 (70.8)	
Primary tumor location, n (%)			0.573
Oral cavity	1 (4.0)	1 (4.2)	
Pharyngeal	21 (84.0)	20 (83.3)	
Laryngeal	0 (0)	2 (8.3)	
Others*	3 (12.0)	1 (4.2)	
Cancer stage, n (%)			0.049
III	1 (4.0)	6 (25.0)	
IV (IVA, IVB)	24 (96.0)	18 (75.0)	
Radiotherapy type, n (%)			>0.999
VMAT	20 (80.0)	21 (87.5)	
IMRT	1 (4.0)	0 (0)	
Tomotherapy	4 (16.0)	3 (12.5)	
Total radiation dose, n (%)			0.509
60 Gy	2 (8.0)	0	
66 Gy	2 (8.0)	1 (4.2)	
70 Gy	21 (84.0)	23 (95.8)	
Neoadjuvant chemotherapy, n (%)	23 (92.0)	18 (75.0)	0.138

Data are presented as mean ± SD or n (%). A *t*-test or chi-squared test (Fisher's exact test was used when n < 5) was used to test differences between VFJ and control subjects at baseline. $P < 0.05$ was considered statistically significant. *The primary tumor location category "Others" included parotid cancer (n = 2) and sinonasal cancer (n = 1) in the VFJ group and maxillary sinus cancer (n = 1) in the control group. Abbreviations: CCRT, concurrent chemoradiotherapy; VFJ, vegetable and fruit juice; VMAT, volumetric modulated arc therapy; IMRT, intensity modulation radiation therapy; Gy, gray.

Table 3
Laboratory values, anthropometric data, and nutrient intake between the VFJ and control groups.

Variables	VFJ group (n = 25)		*p*-value[1]	Control group (n = 24)		*p*-value[1]	Change in week 6 of CCRT-Baseline		*p*-value[2]
	Baseline	Week 6 of CCRT		Baseline	Week 6 of CCRT		VFJ group	Control group	
Laboratory data									
WBC (/mm^3)	5882 ± 2284	4805 ± 1759	0.009	5236 ± 2485	4253 ± 1326	0.029	−1077 ± 1729	−983 ± 2036	0.862
TLC (/mm^3)	1459 ± 529	474 ± 263	<0.001	1580 ± 862	495 ± 308	<0.001	−984 ± 570	−1085 ± 848	0.920
Hgb (g/dL)	12.0 ± 1.3	11.3 ± 1.2	0.011	12.5 ± 1.8	11.1 ± 1.6	<0.001	−0.76 ± 1.38	−1.38 ± 1.27	0.107
Alb (g/dL)	4.12 ± 0.35	4.20 ± 0.32	0.214	4.10 ± 0.38	4.13 ± 0.26	0.751	0.08 ± 0.33	0.03 ± 0.38	0.564
TC (mg/dL)	221 ± 51.2	203 ± 54.7	0.063	209 ± 43.8	199 ± 37.0	0.273	−17.9 ± 44.8	−9.7 ± 45.9	0.527
BUN (mg/dL)	20.9 ± 8.3	21.9 ± 9.2	0.467	18.8 ± 5.6	20.9 ± 7.5	0.179	1.02 ± 8.62	2.01 ± 5.99	0.642
CREA (mg/dL)	1.07 ± 0.21	1.14 ± 0.29	0.183	1.12 ± 0.20	1.09 ± 0.21	0.770	0.07 ± 0.22	−0.03 ± 0.22	0.423
hs-CRP (mg/dL)	0.61 ± 1.22	2.05 ± 3.54	0.016	0.34 ± 0.84	1.55 ± 2.56	0.004	1.43 ± 3.56	1.21 ± 2.64	0.992
Anthropometric data									
Body weight (kg)	70.9 ± 14.3	67.0 ± 12.7	<0.001	68.1 ± 11.9	64.0 ± 11.1	<0.001	−3.9 ± 3.2	−4.1 ± 2.9	0.889
BMI (kg/m^2)	25.6 ± 4.49	24.3 ± 4.16	<0.001	24.6 ± 3.29	23.1 ± 3.22	<0.001	−1.38 ± 1.09	−1.44 ± 0.99	0.827
Nutrient intake									
Energy (kcal/day)	1976 ± 237	1648 ± 414	0.002	1900 ± 357	1412 ± 509	0.001	−328.9 ± 480.1	−488.6 ± 612.8	0.314
Vegetable & fruit (servings/day)	3.94 ± 1.87	0.54 ± 1.15	< 0.001	3.60 ± 2.11	1.17 ± 1.42	< 0.001	−3.40 ± 1.91	−2.44 ± 2.49	0.133
VFJ (mL/day)	588 ± 60	486 ± 167	0.004	-	-	-	−102 ± 159	-	-

Data are expressed as mean ± SD. [1]A paired *t*-test was used to examine the differences in laboratory values between baseline and week 6 of CCRT within the intervention and control groups. [2]A *t*-test was used to examine the differences in laboratory values between the intervention and control subjects at baseline and at week 6 of CCRT. The paired *t*-test or Wilcoxon signed-rank test was used to test differences within groups, while the independent *t*-test or Mann–Whitney *U* test was used to determine differences between the control and intervention treatment groups. $P < 0.05$ was considered statistically significant. Abbreviations: VFJ, vegetable and fruit juice; CCRT, concurrent chemoradiotherapy; WBC, white blood cell; TLC, total lymphocyte count; Hgb, hemoglobin; Alb, albumin; TC, total cholesterol; BUN, blood urea nitrogen; CREA, creatinine; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index.

group (86.1% vs 13.9%, p = 0.060). Profiles of all other factors, including age, BW loss, smoking, alcohol consumption, betel nut chewing, number of comorbidities, primary tumor location, cancer stage, radiation dose, and whether the patients received neoadjuvant chemotherapy, between the two groups were not significantly different.

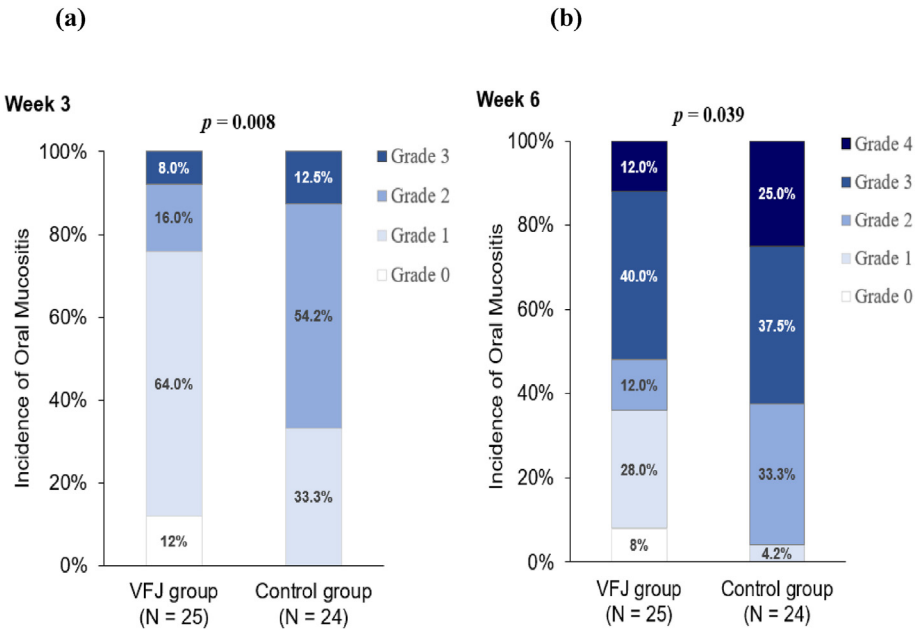

Fig. 1. The incidence of oral mucositis in the VFJ and control groups at week 3 (a) and week 6 (b) of CCRT. The severity of oral mucositis was measured by the WHO scoring system. Data are presented as percentage of subjects. Chi-squared test (Fisher's exact test was used when n < 5) was used to test the differences between the VFJ and control groups. P < 0.05 was considered statistically significant. Abbreviations: CCRT, concurrent chemoradiotherapy; VFJ, vegetable and fruit juice, WHO, World Health Organization.

Table 5 shows that upon adjustment for confounding factors including sex, primary tumor location, radiation dose, and hs-CRP levels, VFJ consumption was significantly correlated with a lower risk of developing ulcerative (grade 2–4) OM (OR 0.063, 95% CI: 0.006–0.635, p = 0.019). Our results suggested that fewer subjects instructed by dieticians and supplemented with daily VFJ during CCRT developed ulcerative OM compared to control subjects who only underwent consultations with the dietician.

3.4. Status of oral pain and dry mouth at the initiation and week 6 of CCRT

As illustrated in Fig. 2a and b, at the initiation of CCRT, the intensity scores of oral pain, and dry mouth were similar between the two treatment groups. After six weeks of CCRT, intensities of oral pain (VFJ: 1.24 ± 0.37 to 2.03 ± 0.70, p < 0.001; control: 1.16 ± 0.27 to 2.95 ± 0.87, p < 0.001) and dry mouth (VFJ: 1.40 ± 0.65 to 2.28 ± 0.74, p < 0.001; control: 1.29 ± 0.46 to 3.00 ± 0.59, p < 0.001) increased significantly from baseline to week 6 of CCRT in both groups. Magnitudes of increase (data not shown) in the intensity of oral pain between VFJ and control groups were 72% and 163% (p < 0.001), respectively, and those in dry mouth were 78% and 158% (p = 0.001), respectively, after six weeks of initiating CCRT. Furthermore, after six weeks of CCRT, in comparison with VFJ group, the control group consistently showed significantly greater intensities of oral pain (2.03 ± 0.70 vs 2.95 ± 0.87, p = 0.001) and dry mouth (2.28 ± 0.74 vs 3.00 ± 0.59, p = 0.001).

4. Discussion

To the best of our knowledge, this is the first clinical study to demonstrate that daily supplementation with 600 mL VFJ is beneficial for alleviating the severity of OM among advanced-stage patients with HNC (stage III–IVB) undergoing CCRT. In the multiple regression analysis, we observed significantly lower risks of ulcerative OM (WHO grade 2–4) in VFJ subjects than in the control subjects (Table 5). This was further confirmed by the observation that VFJ had reduced the intensity of oral pain as well as dry mouth syndrome (Fig. 2). Furthermore, during the routine follow-up by the dietician for all patients, the levels of energy intake at baseline or week 6 of CCRT remained similar between the two groups (Table 3).

Radiation, chemotherapy, and CCRT represent the major three regimens in treating patients with HNC. Chemoradiotherapy-related complications may interfere with cancer therapy; among which chemoradiotherapy-related OM occurs with high incidence and is clinically characterized by mucosal breakdown resulting in deep ulcerations, unbearable oral pain, hyposalivation, and increased risk of secondary infection.[25] CCRT-induced OM is a complex process involving augmented inflammatory responses, reduced cell proliferation, increased cell apoptosis, and impaired regenerative potentials in both mucosal and submucosal compartments.[26] The initiation phase happens immediately after administering the cytotoxic agents, which induce primary tissue damage possibly mediated by elevated intracellular ROS.[11] The message generation stage involves activation of nuclear factor-κB (NF-κB), which subsequently upregulates pro-inflammatory cytokine (TNF-α, IL-1β, and IL-6) production, as well as induces stress-responsive genes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthases (iNOS). The pro-inflammatory cytokines amplify the primary signal and further activate NF-κB, leading to transcription of genes responsible for mitogen-activated protein kinase (MAPK) and tyrosine kinase signaling molecules.[11,26] These signaling pathways collectively cause mucosal injuries. In the ulcerative stage, the basement membrane protective barrier is lost, oral bacteria colonize the ulcer and stimulate surrounding cells to release cytokines and chemokines. This adds more pro-inflammatory reactions, further contributing to cell apoptosis and tissue damage.[27,28]

Almost all patients with HNC receiving RT at a total dose of 60–70 Gy develop some degree of OM, and most of these patients develop severe reactions.[7] The profile of oral pain and xerostomia scores that run parallel with the extent of mucositis and continue to rise as radiation treatment continues.[29] The high incidence of

Table 4
Univariate analysis to assess associations between clinical factors and non-ulcerative and ulcerative oral mucositis at week 6 of CCRT.

Variables	Oral mucositis by the WHO score		*p*-value
	Grade 0–1 (Non-ulcerative)	Grade 2–4 (Ulcerative)	
Age (years)	47.0 ± 11.4	49.9 ± 7.9	0.347
BW loss (%)	−3.8 ± 3.6	−6.0 ± 4.0	0.117
Sex, n (%)			0.620
Male	8 (19.0)	34 (81.0)	
Female	2 (28.6)	5 (71.4)	
Smoking history, n (%)			0.285
Yes	5 (15.6)	27 (84.4)	
No	5 (29.4)	12 (70.6)	
Drinking history, n (%)			0.496
Yes	3 (15.0)	17 (85.0)	
No	7 (24.1)	22 (75.9)	
Betel nut use history, n (%)			0.496
Yes	3 (15.0)	17 (85.6)	
No	7 (24.1)	22 (75.9)	
Comorbidities, n (%)			0.330
2 conditions	2 (50.0)	2 (50.0)	
1 condition	2 (20.0)	8 (80.0)	
None	6 (17.1)	29 (82.9)	
Primary tumor location, n (%)			0.336
Oral cavity	0	2 (100.0)	
Pharyngeal	8 (19.5)	33 (80.5)	
Laryngeal	0	2 (100.0)	
Others	2 (50.0)	2 (50.0)	
Cancer stage, n (%)			>0.999
III	1 (14.3)	6 (85.7)	
IV (IVA, IVB)	9 (21.4)	33 (78.6)	
Total radiation dose, n (%)			0.698
60 Gy	0	2 (100.0)	
66 Gy	1 (33.3)	2 (66.7)	
70 Gy	9 (20.5)	35 (79.5)	
Neoadjuvant chemotherapy, n (%)			0.659
Yes	8 (19.5)	33 (80.5)	
No	2 (25.0)	6 (75.0)	
Hs-CRP at week 6, n (%)			0.060
< 0.1 mg/dL	5 (38.5)	8 (61.5)	
≥ 0.1 mg/dL	5 (13.9)	31 (86.1)	
Group, n (%)			0.011
VFJ	9 (36.0)	16 (64.0)	
Control	1 (4.2)	23 (95.8)	

Data are presented as mean ± SD or n (%). A *t*-test or chi-squared test (Fisher's exact test was used when n < 5) was used to test differences between oral mucositis grade 0–1 and grade 2–4 subjects. $P < 0.05$ was considered statistically significant. Abbreviations: WHO, World Health Organization; VFJ, vegetable and fruit juice; BW, body weight; Gy, gray; hs-CRP, high sensitivity C-reactive protein.

Table 5
Multivariate logistic regression for ulcerative (grade 2–4) oral mucositis using the WHO scale.

Variables	Odds ratio	95% CI	*p*-value
Group (vs. control)	0.063	0.006–0.635	0.019
Sex (vs. Male)	0.961	0.096–9.585	0.973
Primary tumor location (vs. Oral)	0.363	0.068–1.933	0.235
Total radiation dose (vs. 60 Gy)	0.318	0.011–9.470	0.508
hs-CRP (vs. < 0.1 mg/dL)	4.561	0.722–28.797	0.107

P < 0.05 was considered statistically significant. Abbreviations: WHO, World Health Organization; CI, confidence interval; Gy, gray; hs-CRP, high-sensitivity C-reactive protein.

severe OM leads to increased unplanned breaks and delays in radiotherapy, which are invariably associated with poorer treatment outcomes.[30] In a retrospective study conducted by Muzumder et al., symptomatic mucositis (grade ≥ 2) started from week 2, peaked at week 3, continued for 6 weeks, and dropped by week 10.[31] A previous study reported that up to 93.7% of patients with HNC receiving CCRT developed moderate to severe grade (grade ≥ 2) OM, according to the National Cancer Institute–Common Toxicity Criteria grading scales.[32] Herein, the incidence of ulcerative (grade 2–4) OM according to the WHO classification was 64.0% and 95.8% ($p = 0.011$), respectively, among our intervention subjects consuming VFJ and the control subjects (Table 4). The occurrence rate of moderate to severe OM in our control group patients was comparable to those found in a previous study (up to 90%),[32] whereas VFJ supplementation at 600 mL/day lowered the chances of developing moderate to severe grade OM. Beneficial effects of VFJ supplementation in alleviating the extent of oral pain and dry mouth were also established, as patients consuming VFJ consistently showed significantly lower intensities of oral pain and dry mouth at week 6 of CCRT.

Food contains phytochemicals that can affect the antioxidant status of the oral cavity and play a role in oral cavity protection. Botanical-derived antioxidants such as polyphenols are known to scavenge ROS/reactive nitrogen species (RNS), chelate ion and ameliorate side effects via modulating MAPK or NF-κB signaling pathway.[33] Besides, saliva also secrets salivary proteins including immunoglobulins or enzymes that regulate generation of ROS/RNS. The effect of polyphenols binding to salivary proteins, including mucin, can increase the antioxidant activity of lipophilic polyphenols by increasing their solubility.[34] These interactions could allow polyphenols to remain in the oral cavity several hours after consumption.[34] In addition, a previous investigation has shown that the bacterial and fungal oral microbiome changed during

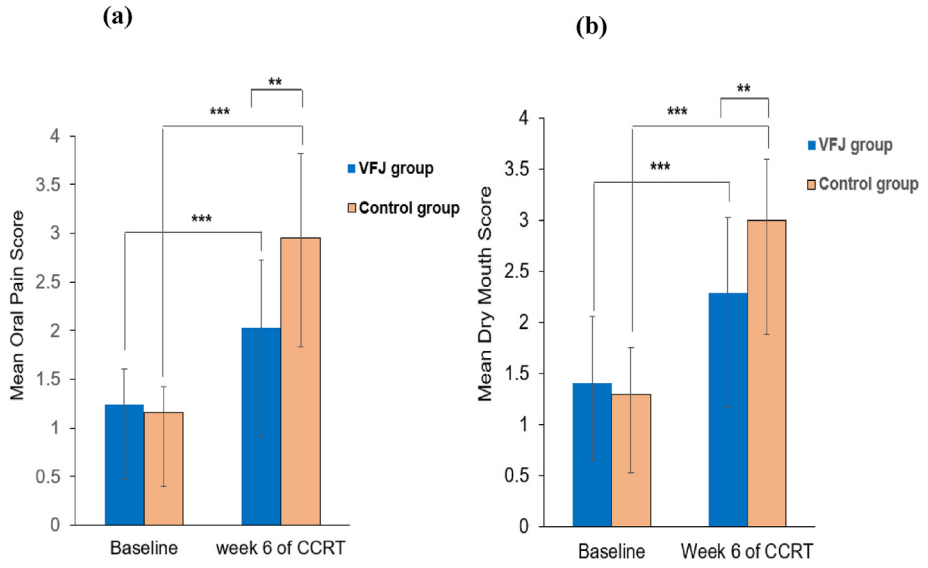

Fig. 2. The mean scores of oral pain (a) and dry mouth (b) at baseline and week 6 of CCRT. Oral pain and dry mouth were assessed based on the EORTC QLQ-H&N35 symptom scales. Data were presented as mean ± SD. The Wilcoxon signed-rank test was used to test differences within groups, whereas the Mann–Whitney *U* test was used to determine differences between the VFJ and control groups. **, $p < 0.01$; ***, $p < 0.001$ were considered statistically significant. Abbreviations: CCRT, concurrent chemoradiotherapy; VFJ, vegetable and fruit juice; EORTC QLQ-H&N35, European Organization for Research and Treatment of Cancer head and neck cancer module.

chemotherapy and strongly correlated with oral mucositis severity.[35] For example, streptococcus species are found mostly in the oral cavity and nasopharynx, forming a significant portion of the normal microbiota of humans. Under an immune-compromised environment, they may cause infection.[36] Findings from previous studies indicate that phytochemicals may be beneficial in eliminating infections while having minimal side effects due to bactericidal or bacteriostatic effects, preclusion of bacterial adherence to mucosal surfaces, and lessening the formation of biofilm and plaque.[37,38]

Changes in caloric intake between the VFJ and control groups were similar. Excluding the amount of VFJ consumed, both groups consumed a similar amount of fruit and vegetables (servings/day) derived from their regular diet at baseline and week 6 of CCRT. However, the VFJ group had additional VFJ consumption at an average of 538 ± 62 mL/day during the entire intervention period. Thus, it is plausible that phytochemicals, such as the polyphenols and carotenoids contained in the VFJ, may modulate the risk of mucositis development. A review article indicated that carotenoids and polyphenols may be used to reduce the side effects of chemotherapy and radiotherapy and reduce the occurrence of second primary cancers.[39] Polyphenols intake is known to mitigate cancer risk, depending on the cancer sites, specific polyphenols examined, and accurate evaluation of dietary exposure.[40] Due to its anti-inflammatory effect, the use of a mouthwash with added plant natural agents rich in polyphenols has been shown to be promising in healing cancer therapy-induced OM.[12] Fibroblasts have been suggested to play an important role in wound healing in oral ulcers. Tsai et al. found that citrus polyphenols could induce the proliferation and migration of fibroblast cells, accelerating the healing time of oral ulcers.[41]

One clinical study investigated the effect of β-carotene supplementation (250 mg daily up to day 21, followed by 75 mg daily for the duration of treatment) in patients with advanced squamous carcinoma of the mouth who were receiving CCRT; after six weeks, the incidence of severe (grade 3–4) mucositis was lower in patients receiving β-carotene supplementation than in those receiving placebo ($p < 0.025$).[42] Meyer et al. also conducted a prospective study with 540 patients with HNSCC and found that subjects with higher dietary intakes of β-carotene had fewer severe acute adverse effects induced by RT (OR 0.61, 95% CI: 0.40–0.93).[43] In addition to β-carotene, intraperitoneal injection of lycopene to rats has been reported to alleviate the severity of oral mucositis after irradiation. Injection of lycopene before and after irradiation reduced the radiation-induced oxidative damage by augmenting antioxidant enzyme activities and reducing peroxidation of membrane lipids.[44] The effect of individual consumption of vegetables and fruits on the total antioxidant potential of the human body does not appear to be attributable to a single antioxidant, but it possibly depends on the synergistic action and mutual interactions between different antioxidants (especially non-vitamin antioxidants) present in food.[45] In this study, the VFJ used multiple fresh vegetables and fruits, which included some non-edible peels, seeds, and young leaves (Table 1a), retained ample amounts of total polyphenols and carotenoids (particularly rich in β-carotene and lycopene) in the vegetables and fruits used (Table 1b).

Radiotherapy alone or in combination with chemotherapy may induce the development of acute mucositis, which is a result of tissue injury induced by cell apoptosis, leading to increased release of pro-inflammatory cytokines. The acute-phase reaction represents systemic adaptation changes in response to tissue injury, and changes in acute-phase proteins may reflect inflammation intensity.[46] CRP can rapidly react, and its level can significantly increase by a thousand-fold within hours of initiation of the inflammatory process.[47] It has also been indicated as an objective measure to study the complexities of radiation mucositis, which is documented as one of the worst side effects of HNC therapy.[48] Ki et al. reported significant correlations between changes in CRP levels and progression of the mean grade of mucositis according to the radiation fraction number among advanced stages of patients with HNC receiving total radiation doses ranging from 70.0 to 74.2 Gy in 35 fractions.[49]

Mohammed et al. performed a weekly examination of acute-phase protein profiles, including erythrocyte sedimentation rate and CRP, among 62 patients with HNC receiving RT alone or in combination with CT, with prescribed radiation doses ranging from 50–70 Gy. CRP levels increased significantly at week 6 and continued to reach the maximum at week 8, with values 3.4-fold

higher compared to the baseline.[50] Similarly, our results showed a significant increase of hs-CRP level in both the treatment groups when CCRT treatment continued up to six weeks (Table 3). Those with hs-CRP level $\geq$ 0.1 mg/dL at week 6, as opposed to < 0.1 mg/dL, correlated with increased risks of grade 2–4 ulcerative OM, although the differences only reached marginal significance. Results of our studies and previous findings illustrated profiles of CRP to be parallel with the development of OM.[48,49] After supplementation of VFJ during 6-week CCRT, changes of hs-CRP did not differ from the control group. It implies that supplementation of VFJ consumption to alleviate the development of ulcerative OM may not be mediated by modulating the production of pro-inflammatory mediator, hs-CRP. Future studies with a longer follow-up period will be needed to further explore the related mechanisms.

Most patients with HNC receiving CCRT develop severe OM manifested as deep and very painful ulcerative lesions of the oral mucosa, which impede physiological functions such as nutrition or swallowing.[8] Previous investigations have shown that adequate nutritional support during radiotherapy or CCRT can alleviate the impact of side effects as well as minimize weight loss and impaired nutrient intake.[51,52] Three studies explored the impact of nutritional intervention, i.e., nutrition counseling plus oral nutrition supplement (ONS) compared to standard care and showed that the weight loss magnitude (kg) in the nutrition support group ranged from 0.5 to 3.7 kg at week 8 among HNC patients receiving at least 20 fractions of radiotherapy.[51–53] One recent study enrolled patients in all stages of HNC who received radiotherapy at a dose of 30–70 Gy and compared the effects of nutrition counseling only (39.5% CCRT) or nutrition counseling plus ONS (29.5% CCRT) on various nutritional indicators.[54] At the end of radiotherapy, the mean changes in weight loss (kg) in the modified-intention-to-treat population were −1.9 kg in the counseling plus ONS group and −3.5 kg in the nutrition-counseling group. In our study, both groups of patients belonged to stages III–IVB and all received CCRT with radiotherapy at a dose of 60–70 Gy. Both groups of subjects received face-to-face nutrition counseling before CCRT and were followed up weekly by dieticians via telephone; changes in mean body weight loss were 3.9 kg in the VFJ group and 4.1 kg in the control group (Table 3). Compared to previous reports,[51–54] the cancer stage severity, radiotherapy dose, and percentage of CCRT were all advanced in our study group. Thus, the extent of weight loss in both groups was reasonable. Furthermore, as indicated by other studies, some routinely assessed blood markers including WBC, TLC, Hgb, and Alb decrease in patients with HNSCC ($\geq$ 65 years) undergoing chemoradiotherapy.[55] In our study, we also observed reductions in the WBC, TLC, and Hgb levels in both groups of subjects from baseline to week 6 of CCRT. However, the changes in these blood markers, including WBC, TLC, and Hgb, remained similar between the two groups (Table 3). The other biochemical data, including Alb, TC, BUN, and CREA, did not change within each group, demonstrating that there were no adverse effects on serum clinical chemistry parameters related to VFJ consumption. Therefore, our study results, along with other investigations,[51,53–55] all imply that nutrition support must be provided before and throughout radiotherapy to assist in the successful completion of the required cancer treatment.

In traditional Chinese medicine, food attributes (hot, warm, neutral, cool, cold) are parts of dietary therapy. According to the hot and cold theory, 'hot/warm' foods were known to associate with metabolism and sympathetic nervous system enhancement, vasodilatory and pro-inflammatory effects. In contrast, 'cold/cool' foods with lower oxidation potential and anti-inflammatory properties may play roles in detoxification/elimination processes.[56] In our VFJ, raw and fresh foods consisted attributes with cold/cool (beetroot, celery, cucumber, alfalfa sprouts, tomato, apple, orange, and lemon), neutral (carrot, pineapple, and Chinese wolfberry), and warm (guava).[56,57] Future research into metabolomics may provide additional quantifiable evidence to verify these ancient classifications of 'hot/warm' or 'cold/cool' attributes, as well as additional therapy possibilities.

Care costs including pain management treatments, gastrostomy tube placement or total parenteral nutrition, and unplanned hospitalizations due to infection would increase the medical expenses. Elting et al. demonstrated that CCRT-induced OM grades 1–2 and grades 3–4 were accompanied by a US $2,200 – $2,400 and $4,600 – $4,900, respectively, increase in costs compared with those patients without OM.[32] Furthermore, a study also indicated that an additional medical cost of CCRT-induced OM was approximately $17,000 per patient treated for head and neck cancers.[58] In our study, the total expenses for preparing VFJ for 8-week would be approximately $47. It is quite evident that our freshly made VFJ not only serves as a healthy and safe dietary regimen, but also as an effective and economical care strategy.

Our study has some limitations. First, this study was not a randomized controlled trial, rather, it had a quasi-experimental design with small sample size. Secondly, we did not measure dietary biomarkers in blood to assess phytochemical-rich VFJ intakes. Except for hs-CRP, no intermediate biomarkers such as anti-oxidative enzymes or oxidative-stress indicators in serum or saliva were analyzed in HNC patients. Finally, results of this study may not be generalizable to other cancers because HNC patients are more susceptible to developing OM. Further interventional studies with longer durations are needed to validate the long-term impact of VFJ on the recovery of nutrition and mucositis status after CCRT completion.

5. Conclusions

The protective role of phytochemicals in mitigating the risk of oral mucositis development may be attributed to their effects of anti-oxidation, reducing peroxidation of membrane lipids, and promoting oral wound healing. In our study, the freshly blended vegetable and fruit juice contained ample amounts of phytochemicals such as total polyphenols, β-carotene, and lycopene. Consumption of the phytochemical-rich VFJ was significantly correlated with a lower risk of grade $\geq$ 2 CCRT-induced OM. Therefore, freshly made VFJ appears to be a healthy, safe, economical and effective dietary strategy to alleviate the severity of oral mucositis in patients with locally advanced head and neck cancer.

Data availability statement

The data generated during this study is confidential and the deidentified participant data is available upon reasonable request from the corresponding author.

Author contributions

HPC, YPL, and YJC designed the study. HPC and YPL obtained the funding. HPC, YJC, YPL, and CWW carried out the recruitment and data collection. HPC and MCH did the statistical analysis. HPC and MCH drafted the manuscript. LYS supervised the project and reviewed the manuscript. All authors have read and approved the manuscript.

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Declaration of competing interest

None of the authors has any conflict of interest.

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