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Original Article

Bao Yuan Gao vs. Calendula cream for radiotherapy-induced skin toxicity in head and neck cancer: A randomized controlled trial

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ABSTRACT

Background and purpose: Radiation Dermatitis (RD) is a frequent side effect in head and neck cancer (HNC) patients undergoing radiotherapy, negatively affecting their quality of life. Topical treatments are used for RD management, but many lack robust evidence of efficacy.

Methods: This randomized controlled trial compared the effectiveness of Bao Yuan Gao, a traditional Chinese herbal ointment, with Calendula cream, a cortisone-free topical agent, in preventing severe acute RD in HNC patients. Fifty-five patients receiving radiotherapy (60–70 Gy) with or without concurrent chemotherapy were randomized to apply either Bao Yuan Gao or Calendula cream three times daily throughout their treatment and two weeks post-treatment. RD severity was assessed weekly using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and skin condition changes were monitored bi-weekly.

Results: Of the 55 enrolled patients, 50 completed the study. While the incidence of grade ≥ 2 dermatitis did not differ significantly between groups, Bao Yuan Gao significantly reduced erythema and improved skin moisture at week 3 ($p = 0.02$). Favorable trends were also observed in sensitivity, melanin deposition, pain, and reduced nutritional support needs.

Conclusion: Bao Yuan Gao yielded measurable skin-protective effects, suggesting potential benefits beyond Calendula. These findings, aligned with its anti-inflammatory herbal properties, support further investigation in larger, dose-controlled trials.

Introduction

Treatment modalities for head and neck cancer mainly encompass surgery, radiotherapy and chemotherapy, with the latter frequently resulting in adverse effects such as Radiation Dermatitis (RD) and oral mucositis [1]. Risk factors for RD include both treatment-specific elements, such as radiation dose and the anatomical site exposed [2], and patient-specific factors, including comorbid diseases [3], obesity, age, gender, sun exposure, and smoking [4]. Additionally, certain chemotherapeutic agents and EGFR inhibitors, like anthracyclines or taxanes, can significantly elevate the risk of severe RD [5].

The general management of RD involves both preventive strategies and medical intervention. Daily preventive measures include maintaining the treated area clean and dry, gently washing with warm water

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and mild soap, avoiding irritants, wearing loose clothing, and minimizing skin abrasions [6]. Recommended topical treatments include glucocorticoids, Vaseline, olive oil, ascorbic acid, and sulfadiazine to alleviate symptoms and promote healing [6]. The Multinational Association of Supportive Care in Cancer (MASCC) recently published international Delphi consensus-based guidelines that highlighted the unmet need for non-invasive and non-steroid approached, recommending only silicone-based film, hydrofilm and olive oil [7].

Specific herbs and compounds, such as aloe, moist burn ointment, and Kangfuxin liquid, enhance tissue regeneration and blood circulation around wounds [8–10]. Additionally, turmeric's curcumin [11] and compound ulcer oil can modulate inflammatory responses and promote healing by affecting various cytokines and growth factors, thus improving recovery rates from skin inflammation [12].

Bao Yuan Gao, derived from Shengji Yuhong Gao, is a traditional Chinese ointment used to promote skin and muscle regeneration, invigorate blood, and detoxify. This remedy, originating from the "Orthodox Manual of External Diseases," includes ingredients like *Angelica dahurica*, Glycyrrhiza, *Angelica sinensis*, Arnebiae Radix, and others, aimed at treating skin ulcers and other infections [13]. The ointment is primarily used to invigorate blood, clear decay, detoxify, and promote the regeneration of tissues. It's specifically formulated for the treatment of ulcers, carbuncles, and other infected wounds [14–16].

Calendula officinalis, a natural cortisone-free cream, proved safe and maintained skin moisture effectively, it significantly reduced the incidence of ARD compared to patients using commercial trolamine in a phase III randomized trial [17].

The current study investigated the use of Bao Yuan Gao as a topical treatment for RD, focusing on its preventative capabilities. The findings disclosed the ointment's effectiveness in adhering to the principles of preemptive care and provided substantial evidence-based support for its use in treating radiation-induced skin reactions.

Materials and methods

Study design

This was a single center, randomized, controlled trial conducted at the Far Eastern Memorial Hospital, adopting a non-inferiority design hypothesizing that Bao Yuan Gao would not be inferior to Calendula cream in preventing grade ≥ 2 radiation dermatitis. This study did not involve a formal non-inferiority sample size calculation. The sample size was determined pragmatically based on clinical feasibility, and as such, the study may be underpowered to detect small differences in non-inferiority comparisons. Randomization was performed using a computer-generated sequence, with allocation concealment ensured through sequentially numbered, opaque, sealed envelopes. Both topical agents were dispensed in identical opaque containers labeled only with participant codes. While the appearance, texture, and scent of the two preparations differed, neither the participants nor the research personnel who interacted with them were informed of the group assignment. Although these individuals could potentially infer treatment based on sensory characteristics, they did not have access to the decoding key. Only the study analysts were granted access to the group assignment table during data analysis.

Therefore, the trial employed a blinded analysis design, wherein participants and interacting personnel were unaware of the treatment group labels' true meaning, and outcome assessors/statisticians remained blinded until database lock and final analysis.

Patient population

Patients eligible for the study were aged 20 to 80 years, diagnosed with HNC, and scheduled for definitive radiotherapy (70 Gy) or adjuvant RT (60–66 Gy) with or without concurrent chemotherapy. Exclusion criteria included pre-existing skin conditions, allergies to Calendula cream, use of glucocorticoids, immunosuppressants, or amifostine, prior head and neck RT (except for radioactive iodine therapy), pregnancy, lactation, and concurrent primary malignancies.

Ethical considerations

The study was approved by the Institutional Review Board of Far Eastern Memorial Hospital (FEMHIRB,108114-F). The Bao Yuan Gao and Calendula cream were sourced from Glorious Jewel Group, Taipei, Taiwan and Pommade au Calendula par Digestion; Boiron Ltd, Levallois-Perret, France, respectively. Participants provided informed consent, and the trial was conducted in compliance with ethical standards.

Randomization

Participants were randomly assigned to either the Bao Yuan Gao or Calendula cream group, applying their assigned cream three times daily during RT and for two weeks post-treatment. The study was double-blinded, and assessments were performed by clinicians unaware of the group assignments.

Radiation therapy and chemotherapy

All patients received external beam radiation therapy using either VMAT or Helical Tomotherapy (HT), both utilizing 6-MV photon beams. VMAT was delivered via two full arcs on a Versa HD linear accelerator (Elekta Oncology Systems, Crawley, UK). HT was performed on a TomoTherapy system (Accuray, Sunnyvale, CA), with field width 2.5 cm, pitch 0.287, and modulation factor (MF) 3.0. Prescribed doses ranged from 60 to 70 Gy in 33 to 35 fractions. [18,19]. Concurrent chemotherapy, when administered, consisted of weekly cisplatin (30 mg/m^2) plus fluorouracil and leucovorin [20] (Table 2).

Study outcomes

Radiation dermatitis was assessed weekly using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The maximum observed RD grade per patient was recorded, and the incidence of grade ≥ 2 and grade ≥ 3 RD was compared between the two groups. Skin condition changes, such as erythema, sensitivity, moisture, oiliness, and pigment deposition, were monitored bi-weekly using an API mobile skin analyzer. Quality of life was assessed using the EORTC QLQ-H&N35 questionnaire. The primary outcome was the incidence of grade ≥ 2 RD. Secondary outcomes included quality of life measures and the severity of skin reactions.

The data was adjusted to baseline values and displayed as a "ratio of change" using the formula: Ratio of Change = (Skin measurement index at Week X / Skin measurement index at Baseline). This method quantified changes in skin condition over time relative to the initial measurements.

Statistical methods

Data were presented as percentages, medians, or means ± standard error of measurement (SEM). Categorical variables were compared using chi-square or Fisher's exact tests, while continuous variables were analyzed using the Mann-Whitney *U* test. Kaplan-Meier analysis estimated the time to grade ≥ 2 RD, with group comparisons made via the log-rank test. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS software (Version 20.0, IBM Corporation, Armonk, NY, USA) or Prism 10 (GraphPad Software, Boston, MA, USA) at the Data Center.

Results

Between November 2019 and January 2022, a total of 55 patients

were randomly assigned to either the Bao Yuan Gao group (30 patients) or the Calendula creamgroup (25 patients) as shown in Fig. 1. Following the specified exclusions, 50 patients finished the study and were included in the analysis. Two patients were excluded due to loss to follow-up before completing treatment.

Demographic and clinical characteristics are summarized in Table 1. The baseline characteristics were fairly balanced between both groups. The median ages were 52.5 years (range 27–68) for the Bao Yuan Gao group and 49.0 years (range 36–74) for the Calendula group. A statistically significant difference in gender distribution was noted between groups ($p = 0.003$), with all patients in the Bao Yuan Gao group being male compared to 70.8 % in the Calendula group. The most common tumor location in both groups was the oral cavity, comprising 50.0 % in the Bao Yuan Gao group and 57.7 % in the Calendula group, followed by nasopharynxx at 23.1 % and 41.7 %, respectively, and other locations at 19.1 % and 8.4 %. There was a roughly equal distribution of AJCC stages between the two groups. Specifically, Stage IV patients numbered 20 in the Bao Yuan Gao group and 17 in the Calendula group; Stage II and III patients totaled 6 and 5 in the Bao Yuan Gao and Calendula groups, respectively. There was no statistically significant difference in stage distribution ($p = 0.084$). Usage rates of tobacco, alcohol, and areca nut were 76.9 %, 50 %, and 11 % in the Bao Yuan Gao group, compared to 54.2 %, 33.3 %, and 33.3 % in the Calendula group, respectively.

All patients completed their assigned RT regimen, with 100 % of the Bao Yuan Gao group and 87.5 % of the Calendula group receiving concurrent chemotherapy ($p = 0.063$). Both groups received a median prescribed dose of 70 Gy, with a range of 60–70 Gy. All plans were approved based on the criterion that 95 % of the planning target volume (PTV) was covered by 100 % of the prescribed dose. The distribution of radiation techniques was as follows: 53.8 % of the study group versus 37.5 % of the control group were treated with volumetric modulated arc therapy (VMAT), and 46.2 % versus 62.5 % received Helical Tomotherapy (HT), respectively ($p = 0.247$) (**Supple. Table 1**).

The incidence of grade ≥ 2 radiation dermatitis was 69.2 % in the Bao Yuan Gao group and 56.0 % in the Calendula group ($p = 0.207$). Grade ≥ 3 RD occurred in 42.3 % of Bao Yuan Gao users and 36.0 % of Calendula users ($p = 0.332$) (**Supple. Table 2**). In both groups, the median onset of grade ≥ 2 and grade ≥ 3 radiation dermatitis was observed in the fifth and seventh weeks of radiotherapy, respectively. (**Supple. Table 2**). The cumulative incidence of grade ≥ 2 or ≥ 3 radiation dermatitis showed no significant differences between the groups (Fig. 2**A–B**).

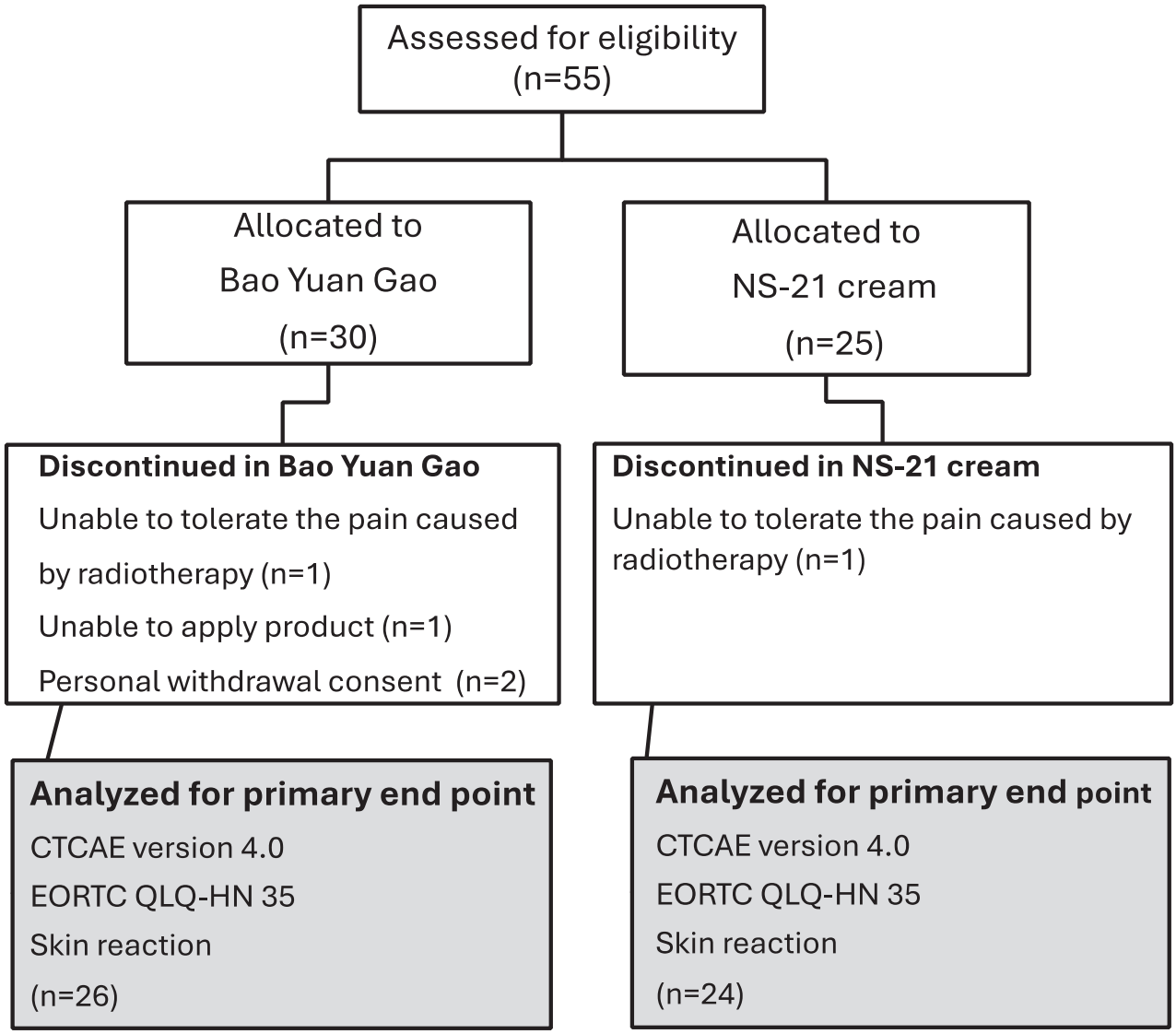

Fig. 1. CONSORT diagram depicting the random assignment of participants to the study groups. Participants were randomized at an allocation ratio close to 1:1 between receiving basic nursing care with Bao Yuan Gao treatment or CALENDULA with a placebo (control group). Two participants discontinued the study—one due to withdrawal of consent and one due to a non-treatment-related adverse event.

Table 1
Study characteristics.

Characteristic	Bao Yuan Gao	CALENDULA	*P value*
	n = 26	n = 24	
Age			0.281
Median (range), year	52.5 (27–68)	49.0 (36–74)	
Gender			0.003
Male, n (%)	26 (100 %)	17 (70.8 %)	
Female, n (%)	0 (0 %)	7 (29.2 %)	
Tumor site, n (%)			0.609
Oral cavity cancer	15 (50.0 %)	12 (57.7 %)	
NPC	6 (23.1 %)	10 (41.7 %)	
Hypopharyngeal cancer	1 (3.8 %)	1 (4.2 %)	
Oropharyngeal cancer	2 (7.7 %)	1 (4.2 %)	
Nasal cavity cancer	1 (3.8 %)	0 (0 %)	
Laryngeal cancer	1 (3.8 %)	0 (0 %)	
TNM Classification			
T			0.059
T1	2 (7.7 %)	7 (29.2 %)	
T2	5 (19.2 %)	7 (29.2 %)	
T3	10 (38.5 %)	3 (12.5 %)	
T4a	4 (15.4 %)	3 (12.5 %)	
T4b	3 (11.5 %)	0 (0 %)	
T4	2 (7.7 %)	4 (16.7 %)	
N			0.407
N0	6 (23.1 %)	6 (25.0 %)	
N1	3 (11.5 %)	2 (8.3 %)	
N2	8 (30.8 %)	12 (50.0 %)	
N3	9 (34.6 %)	4 (16.7 %)	
M			N.A.
M0	26 (100 %)	24 (100 %)	
M1	0 (0 %)	0 (0 %)	
AJCC (7th edition) Stage			0.084
I	0 (0 %)	2 (8.3 %)	
II	1(3.8 %)	4 (16.7 %)	
III	5 (19.2 %)	1 (4.2 %)	
IV	20 (76.9 %)	17 (70.8 %)	
Education			0.647
Primary School	3 (11.5 %)	2 (8.3 %)	
Junior high school	8 (30.8 %)	8 (33.3 %)	
High school	10 (38.5 %)	8 (33.3 %)	
Vocational college	3 (11.5 %)	2 (8.3 %)	
Undergraduate	1 (3.8 %)	4 (16.7 %)	
Graduate	1 (3.8 %)	0 (0 %)	
Marital status			0.363
Sigle	6 (23.1 %)	2 (8.3 %)	
Married	18 (69.2 %)	20 (83.3 %)	
Divorced	2 (7.7 %)	2 (8.3 %)	
Tobacco-smoking history			0.09
Yes	20 (76.9 %)	13 (54.2 %)	
No	6 (23.1 %)	11 (45.8 %)	
History of alcohol use			0.233
Yes	13 (50 %)	8 (33.3 %)	
No	13 (50 %)	16 (66.7 %)	
History of areca nut			0.514
Yes	11 (42.3 %)	8 (33.3 %)	
No	15 (57.7 %)	16 (66.7 %)	

The impact of Bao Yuan Gao for radiation dermatitis protection on patient quality of life was evaluated using the H&N35 score at baseline (week 0) and at various points during and after radiotherapy (weeks 1 to 11). Radiation-induced acute skin reactions were quantified as the mean ± SD over the study period (Table 2). Typically, skin reactions in both groups followed a similar pattern, with a peak typically occurring within the first week post-radiation. Symptoms generally worsened progressively, with the most significant relative change in skin condition observed around the fifth or seventh week, followed by recovery four weeks after the completion of therapy (**Fig. 3A–H**).

In the left neck, Bao Yuan Gao significantly reduced erythema/sensitivity reactions at week 3 (during radiotherapy) and week 11 (four weeks post-radiotherapy). Bao Yuan Gao also tended to result in lower erythema/sensitivity scores from week 1 to week 11 compared to the Calendula group, though the difference was not statistically significant ($p < 0.074$) (Fig. 3**A**). However, no differences were observed between the two groups in the right neck (Fig. 3**B**).

Regarding skin moisture, there was a significant difference in the left neck at week 3 between subjects using Bao Yuan Gao and those using Calendula, with both groups showing similar patterns in the right neck (Fig. 3**C–D**). In contrast, the results for skin oiliness displayed reverse trends, where dry desquamation (less moisture) correlated with increased oiliness (Fig. 3**E–F**).

Furthermore, Bao Yuan Gao was associated with significantly higher scores of skin melanin pigment deposition in the left neck at week 1 and throughout the period from week 1 to week 11 ($p = 0.03$) (Fig. 3**G**). However, there were no significant differences between the two groups in the right neck (Fig. 3**H**).

The impact of the radiation dermatitis protecting herbal products, Bao Yuan Gao and Calendula, on patient quality of life was measured using the H&N35 score at baseline, bi-weekly during radiotherapy, and at weeks 2 and 4 post-radiotherapy, as detailed in **Supple. Table 3**.

Throughout the study period, patients in the Bao Yuan Gao group generally reported better pain scores compared to the Calendula group, with statistical significance noted at weeks 3 ($p = 0.07$) and 5 (Fig. 4). There were no statistically significant differences observed in other symptoms such as swallowing, dental issues, jaw opening, and sensory experiences (**Supple Fig. 1**A–D). Moreover, no significant differences were found between the two groups in terms of speech, social eating, social contact, sexuality, disease awareness, and use of pain medications (**Supple Fig. 2**A–F). However, a significant difference was noted at week 1 in sexuality (**Supple Fig. 2**D). Patients using Bao Yuan Gao reported less frequent use of nutritional supplements throughout the study period ($p < 0.013$), with specific differences emerging at weeks 5 and 7 (**Supple Fig. 3**A). There were no significant differences in terms of feeding tube usage, weight loss, or weight gain between the groups (**Supple Fig. 3**B–**D**).

Discussions

This randomized controlled trial evaluated the efficacy of Bao Yuan Gao in preventing Acute Radiation Dermatitis (ARD) in patients with head and neck cancer receiving radiotherapy. Although the incidence of grade ≥ 2 ARD was not significantly different between the Bao Yuan Gao and Calendula groups, Bao Yuan Gao demonstrated measurable clinical advantages across multiple parameters. These included a statistically significant reduction in erythema and improved moisture retention in the left neck area, particularly at week 3 ($p = 0.02$ for both endpoints), and a consistent trend favoring reduced skin sensitivity throughout treatment. Additionally, the left-sided erythema scores showed a more sustained reduction throughout the treatment course in the Bao Yuan Gao group. While these findings should be interpreted with caution given the study size, they support the possibility that Bao Yuan Gao provides superior symptomatic relief and skin barrier protection compared to Calendula.

Bao Yuan Gao, a traditional Chinese herbal ointment derived from Shengji Yuhong Gao, contains ingredients such as *Angelica dahurica*, *Angelica sinensis*, *Arnebiae Radix*, *Resina Draconis*, and sesame oil. These components have well-documented anti-inflammatory, antioxidant, and wound-healing properties. Specifically, *Angelica sinensis* polysaccharides have been shown to promote hematopoiesis and tissue repair [21,24], while *Angelica dahurica* modulates key inflammatory pathways including NF-κB and COX-2 [22,25]. Shikonin from *Lithospermi Radix* facilitates granulation and neovascularization [23,26], and *Resina Draconis* enhances dermal repair by improving tensile strength and vascular density [24,31]. Sesame oil further contributes to skin moisture retention and pain relief [25,26,[25,26,33,35]. The bioactivity of these herbal compounds may underlie the observed clinical improvements in erythema and skin integrity in Bao Yuan Gao users.

The mechanisms underlying radiation-induced skin reactions (RISRs) involve a complex interplay between inflammatory responses and oxidative stress (OS) [22,27]. These two processes interact and

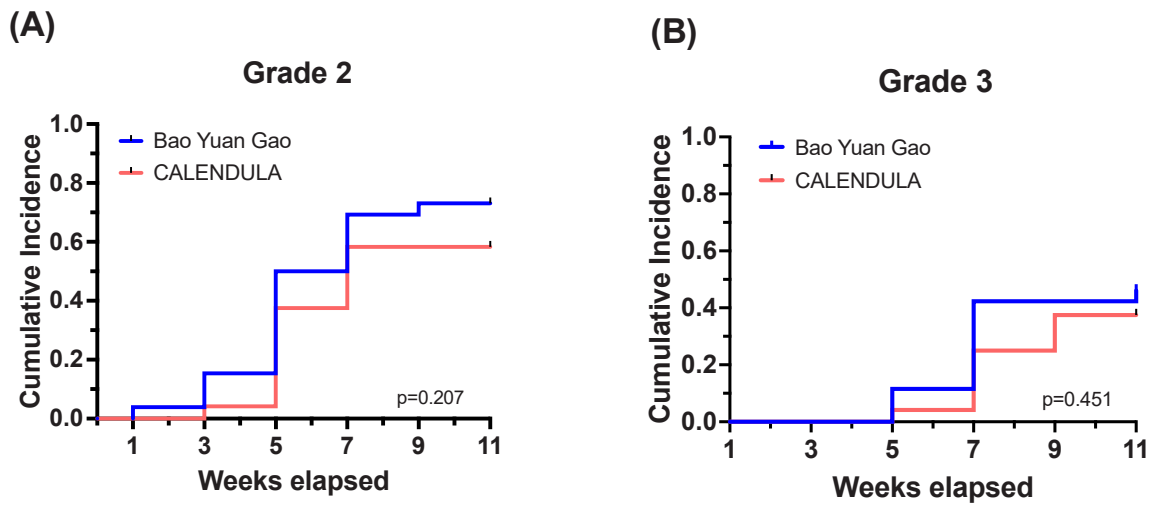

Fig. 2. (A) Cumulative Incidence of Grade ≥ 2 Radiation Dermatitis, (B) Cumulative Incidence of Grade ≥ 3 Radiation Dermatitis.

Table 2
Occurrence and progression of skin reactions over the duration of the study.

Skin reactions								
After RT Week1-Week 11 (Avg. ± SD)	**Bao Yuan Gao**			**CALENDULA**			***P* value**	
							Week 1-Week 11	specific time point (week)
Skin moisture								
Left	0.80	±	0.18	0.67	±	0.16	NS	3 ($p = 0.02$)
Right	0.82	±	0.05	0.98	±	0.06	NS	NS
Oiliness								
Left	4.84	±	1.72	4.78	±	2.07	NS	5 ($p = 0.07$)
Right	3.79	±	0.97	7.74	±	3.55	NS	NS
Erythema/sensitivity								
Left	17.47	±	5.38	30.95	±	6.68	0.0742	3 ($p = 0.03$), 5 ($p = 0.08$), 11 ($p = 0.02$)
Right	22.76	±	5.54	23.31	±	6.97	NS	NS
Melanin pigment deposition								
Left	1.40	±	0.04	1.21	±	0.04	0.0022	1 ($p = 0.03$)
Right	1.11	±	0.03	1.03	±	0.06	NS	NS

enhance each other, creating a cycle that exacerbates the skin damage following radiation exposure. When cells are damaged by radiation, they typically die via mechanisms such as mitotic death, which subsequently triggers inflammation and chronic oxidative stress. In the later stages, this persistent inflammation and oxidative stress can alter cytokine levels, disrupt cell cycle processes, and cause DNA damage, perpetuating the cycle that leads to delayed skin reactions. This ongoing cascade is crucial for understanding the progression and management of radiation-induced skin injuries.

Dry desquamation usually follows at doses of 20 Gy or more, appearing around the fourth week. Moist desquamation, a more severe reaction, tends to occur at doses exceeding 50 Gy, around the fifth to sixth week [21,28]. Our prior research confirmed that the risk of grade 3 Acute Radiation Dermatitis (ARD) was significantly higher for skin receiving doses between 46 to 70 Gy compared to skin exposed to doses of 46 Gy or less ($p < 0.001$) [20].

Management strategies focus on maintaining a moist environment as part of wound care, which helps accelerate healing. In our current study, we demonstrate that Bao Yuan Gao offers a comparable capacity to retain skin moisture. Additionally, we found that Bao Yuan Gao significantly reduced erythema and sensitivity while also minimizing skin moisture loss at week 3 of treatment. Moreover, our data revealed an inverse relationship between skin moisture and the indices of erythema/sensitivity or oiliness. This suggests that, according to the radiotherapy schedule, a higher radiation dose increases erythema and sensitivity, subsequently decreasing skin moisture, which then leads to increased oiliness.

A review of topical Calendula suggests potential benefits in managing radiotherapy-induced skin reactions, though clinical trial outcomes remain inconsistent. Some studies report significant advantages, while others yield inconclusive findings, highlighting uncertainty about Calendula's effectiveness in preventing radiation-induced skin toxicity in radiotherapy patients [23,29]. Furthermore, Calendula's antioxidants, particularly its polyphenolic compounds, have been suggested to help alleviate radiation-induced skin damage. However, clinical support for these claims remains inconsistent, emphasizing the need for more robust research to clarify its efficacy in this area [23,29]. In our analysis, Bao Yuan Gao demonstrated comparable or superior results to Calendula, particularly in erythema control and moisture retention, suggesting it may be a more reliable option for managing radiation-induced skin reactions.

We also observed laterality in skin reactions, with the left side of the neck showing relatively milder symptoms than the right. While this could be due to subtle anatomical or positioning differences during treatment, it is notable that the most pronounced benefits of Bao Yuan Gao were also observed on the left side. This may suggest enhanced efficacy in less inflamed or more stable tissue environments, or possibly a greater ability of Bao Yuan Gao to maintain epidermal integrity under moderate radiation stress. Although speculative, this finding warrants further investigation into localized treatment effects and dose-distribution interactions.

While patients in the Bao Yuan Gao group also reported reduced use

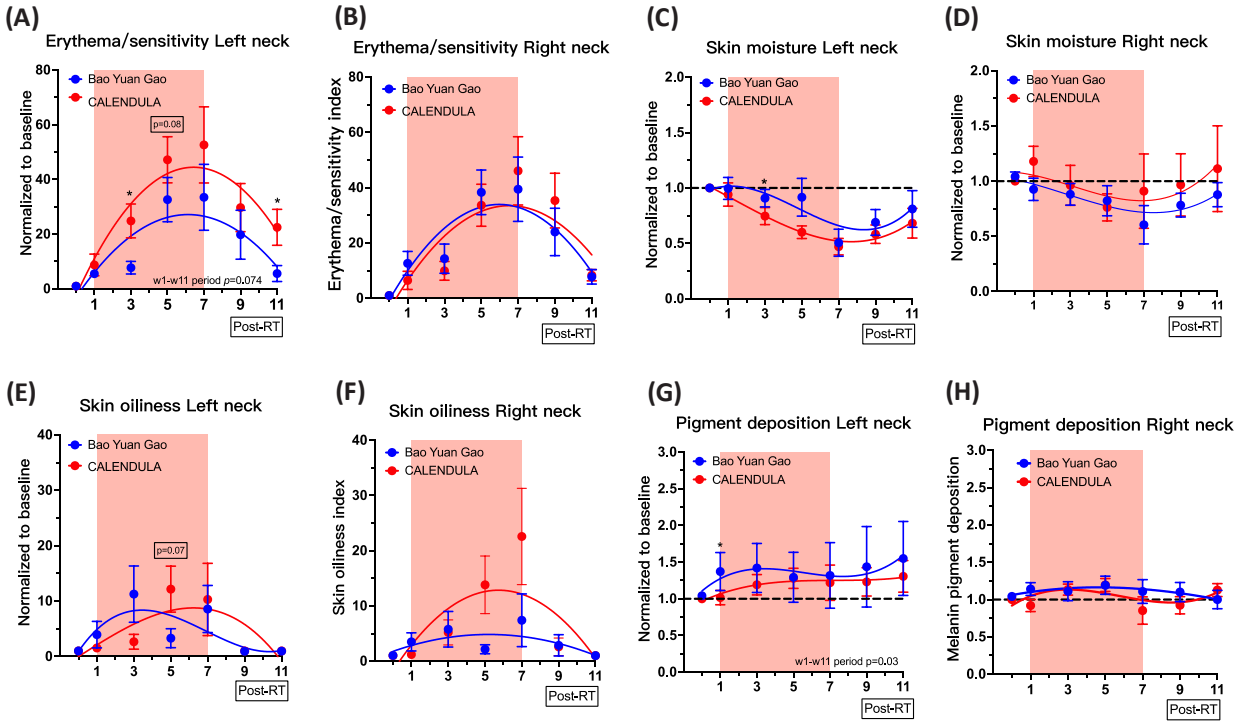

Fig. 3. The changes in the level of skin reaction per group were observed before radiotherapy (week 0), during (weeks 1 to 7), and after radiation therapy completion (weeks 9 and 11). Typically, both groups followed a similar trajectory, with a peak effect commonly occurring within the first week after radiation. Symptoms progressively worsened, reaching a relative maximum ratio of change in skin condition around the fifth or seventh week, followed by recovery four weeks after therapy. (A)-(B) Skin Erythema/Sensitivity, (C)-(D) Skin Moisture, (E)-(F) Skin Oiliness, and (G)-(H) Skin Melanin Pigment Deposition. Data are presented as mean ± SEM; * indicates $p < 0.05$.

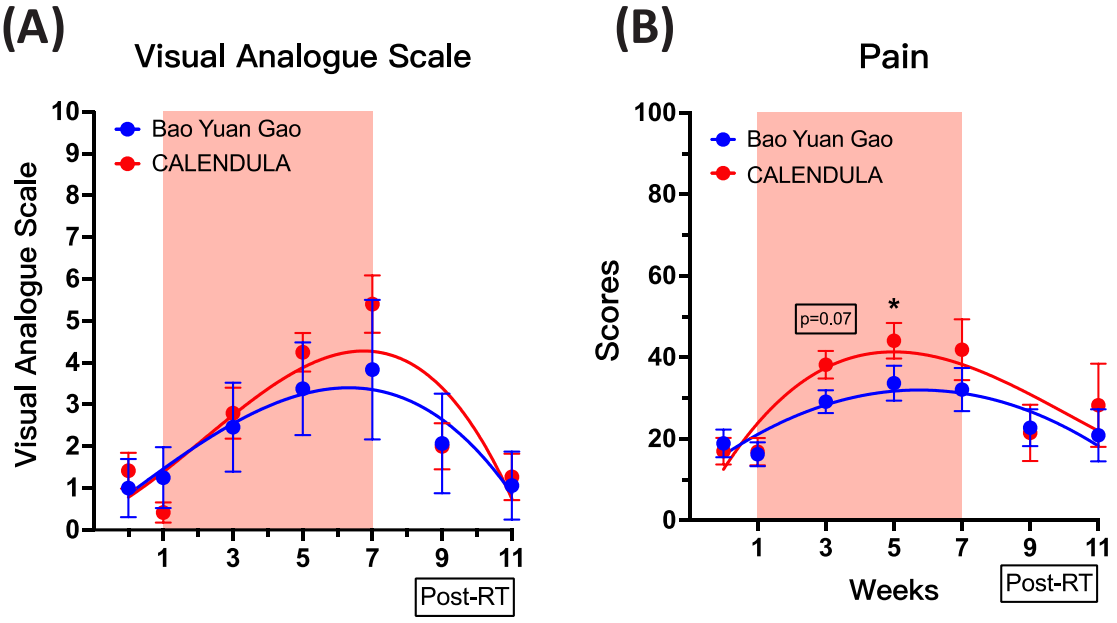

Fig. 4. Patient-reported symptoms of pain were assessed using visual analogue scale (VAS) (A) and HN35 scores (B). HN35 refers to the Head and Neck 35-questions questionnaire. * indicates statistical significance at $p < 0.05$.

of nutritional supplements and showed more stable weight trends, these outcomes did not reach statistical significance and must be interpreted cautiously. Nevertheless, such trends are consistent with the improved skin condition and patient comfort observed in this group. Although the Bao Yuan Gao group demonstrated favorable trends in pain reduction and lower supplement use, these week-specific differences should be interpreted with caution, as they may be subject to temporal variation and reporting bias.

One limitation of this study is the absence of direct skin dose measurements. Differences in radiation delivery techniques, such as VMAT and Helical Tomotherapy (HT), may influence superficial skin dose due to variations in beam modulation and entrance dose characteristics.

Notably, HT may deliver relatively higher surface doses because of its continuous rotational delivery and overlap of entrance and exit beams. While individualized skin dose assessment (e.g., at 2 mm depth) was not performed in this study, we recognize this as a limitation. Future studies should incorporate skin dose-volume histogram (DVH) analyses or direct superficial dosimetry to better characterize the dose–response relationship in radiation dermatitis. This study also has broader limitations. The single-center design and modest sample size limit generalizability and statistical power. While the trial was designed to be double-blind, the different textures and appearances of the two products may have compromised blinding to some extent.

In conclusion, although Bao Yuan Gao did not significantly reduce the overall incidence of grade $\geq$ 2 ARD, it was associated with statistically and clinically meaningful improvements in erythema and skin moisture preservation at specific timepoints. The consistency of these effects, combined with the pharmacological profile of the herbal ingredients, supports its potential as a more effective skin-protective agent during radiotherapy. Compared to Calendula, Bao Yuan Gao may offer enhanced symptomatic relief and improved skin condition, particularly in early to mid-treatment phases. Larger, well-powered, and dosimetry-informed studies are warranted to further validate its clinical utility.

Data Availability

De-identified primary data supporting the findings of this study are available upon reasonable request from the corresponding author.

CRediT authorship contribution statement

Tsang-Ho Ngan: Writing – original draft, Resources, Conceptualization. **Skye Hsin-Hsien Yeh:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis. **Hui-Ju Tien:** Data curation. **Chen-Xiong Hsu:** Data curation. **San-Fang Chou:** Formal analysis. **Chen-Hsi Hsieh:** Writing – review & editing, Methodology, Data curation. **Pei-Wei Shueng:** Writing – review & editing, Resources, Funding acquisition, Data curation.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tsang-Ho Ngan is the President of Glorious Jewel Group and contributed to the redevelopment of Bao Yuan Gao, a classical prescription originating from the Ming Dynasty. The product was manufactured under GMP standards by Sun Ten Pharmaceutical Co., Ltd. Mr. Ngan provided funding and logistical support but was not involved in patient recruitment, data collection, statistical analysis, or interpretation of study results. All other authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110976.

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