Article

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
2014, Vol. 13(3) 201–210

DOI: 10.1177/1534735413503549
ict.sagepub.com
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Suresh Rao, MBBS, MD Radiation Oncology[1], Chetana Dinkar, MDS[1], Lalit Kumar Vaishnav, BAHMS[1], Pratima Rao, MDS[2], Manoj Ponadka Rai, MBBS[1], Raja Fayad, MD[3], and Manjeshwar Shrinath Baliga, MSc, PhD, MBA[4]

Abstract

Purpose. Radiation-induced oral mucositis is an acute morbidity seen in patients undergoing treatment for head and neck cancers. In this study, we evaluated the efficacy of turmeric in preventing radiation-induced mucositis. *Methods*. This was a single-blinded, randomized, controlled clinical trial and was conducted with head and neck cancer patients requiring 70 Gy of radiation or chemoradiotherapy (daily radiotherapy plus carboplatin once a week). Eligible patients (n = 80) were randomly assigned to receive either turmeric gargle (n = 40) or povidone-iodine ([n = 40] active comparator condition) during chemo/radiotherapy during the period of treatment. Oral mucositis was assessed using the RTOG (Radiation Therapy Oncology Group) grading system before the start, during, and at the end of the treatment by an investigator unaware of the treatment. The primary endpoint of this study was the incidence of mucositis every week during the 7-week period. The secondary endpoint was the effect of turmeric gargle on the incidence of treatment breaks, loss of scheduled treatment days, and decrease in body weight at the end of the treatment. *Results*. This study clearly suggests that when compared with the cohorts using povidone-iodine gargle, the group using turmeric as a mouthwash had delayed and reduced the levels of radiation-induced oral mucositis and was statistically significant at all time points ($P < 0.001$ to $P < 0.0001$). Additionally, the cohorts using turmeric had decreased intolerable mucositis ($P < 0.001$) and lesser incidence of treatment breaks in the first half of the treatment schedule before 4 weeks ($P < 0.01$) and reduced change in body weight ($P < 0.001$). *Conclusions*. Gargling with turmeric by head and neck cancer patients undergoing radiation therapy provided significant benefit by delaying and reducing the severity of mucositis. Turmeric is readily available, relatively inexpensive, and highly accepted making it useful in cancer treatment.

Keywords

radiation, mucositis, turmeric, povidone-iodine

Introduction

Oral mucositis, an inflammatory response of the oral–pharyngeal mucosa in response to systemic chemotherapy or from radiotherapy for the head and neck carcinoma is extremely painful and increases morbidity of the patient.[1] Depending on the severity, oral mucositis is grouped as tolerable mucositis (grade 1 and 2 mucositis) and intolerable mucositis (grade 3 or higher).[2] In radiation treatment for the head and neck cancers, tolerable mucositis develops in all patients and is easy to manage.[1,3] However, intolerable mucositis needs additional medical care for effective pain management and may also lead to use of gastrostomy tube or intravenous line for nutritional supplementation.[1,3] At times intolerable mucositis also contributes to dose reduction, dose delay, and even termination of the planned radiation therapy, all of which may consequentially complicate the treatment of the underlying malignancy and cure.[1] Additionally, treatment aimed at ameliorating the complications of mucositis also increases the hospitalization time and the treatment cost.[1,4]

[1]Mangalore Institute of Oncology, Mangalore, Karnataka, India
[2]Century International Institute of Dental Science & Research Center, Poinachi, Kerala, India
[3]University of South Carolina, Columbia, SC, USA
[4]Father Muller Medical College, Mangalore, Karnataka, India

Corresponding Author:
Manjeshwar Shrinath Baliga, Department of Research and Development, Father Muller Medical College, Father Muller Road, Kankanady, Mangalore, Karnataka 575003, India.
Email: msbaliga@gmail.com

The currently available therapies consisting of dental care, use of anti-inflammatory agents, application of topical antiseptics, and antimicrobial agents are essentially palliative, and there is no widely accepted prophylactic or effective treatment for intolerable mucositis.[5] The use of biologicals like the recombinant human KGF-1 (palifermin) although efficacious is very expensive and unaffordable to most patients.[5] Herbal drugs offer an alternative to the synthetic compounds and are considered either nontoxic or less toxic than their synthetic counterparts. Natural products with free radical scavenging, antioxidant, antimicrobial, anti-inflammatory, wound healing, radioprotective, and immunostimulatory properties could be of possible use in the prevention of radiation mucositis and previous studies have shown that honey,[2,6] *Isatis indigotica*,[7] *Leptospermum scoparium*,[8] *Glycyrrhiza glabra*,[9] and *Kunzea ericoides*,[8] possess beneficial effects.

The rhizome of *Curcuma longa* Linn, commonly known as turmeric and belonging to the ginger family, Zingaberaceae is an important spice and a medicinal agent in the various traditional and folk systems of medicine in India, and through different routes of administration, including topically, orally, and by inhalation.[10-13] Turmeric finds mention in the various pharmacopeias as an antiseptic, analgesic, anti-inflammatory, and wound healing agent, and scientific studies have validated these ethnomedicinal properties.[11]

Studies indicate that curcuminoids, which include mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcmin, are the active components and that these phytochemicals like turmeric also possess antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, antimutagenic, immunomodulatory, and wound healing effects.[10-12] Scientific studies have also shown that turmeric/curcumin is effective against various pro-inflammatory diseases and to mediate the beneficial effects by modulating pro-inflammatory cytokines, apoptotic proteins, nuclear factor-κB (NF-κB), cyclooxygenase-2, 5-LOX, STAT3, C-reactive protein, and prostaglandin E(2).[12,13]

Turmeric/curcumin has been extensively investigated for its pharmacological effects on the oral and dental ailments and diseases. Experimental studies have shown that they prevent chemical-induced oral carcinogenesis in experimental animals[14-18] and to induce apoptosis and inhibit cell proliferation of neoplastic cells of head and neck origin.[19-23] Studies have also shown that they are effective in preventing the side effects of anticancer drugs[24-27] and ionizing radiation.[28-31] Turmeric is a frontline wound healing agent in the various traditional systems of medicine and experiments have also shown that turmeric/curcumin were effective in healing wound in different conditions,[32-35] including that of wounds created in mice previously exposed to γ-radiation.[36-39]

With respect to clinical studies, turmeric is shown to be effective as a mouthwash and to possess antiplaque, anti-inflammatory, and antimicrobial properties.[40] Additionally, studies have also shown that the alcoholic extracts of turmeric, turmeric oil, and turmeric oleoresin decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes in patients suffering from oral submucous fibrosis[41] Recently, Chainani-Wu et al[42] have also observed that curcumin was effective in reducing the symptoms and signs of oral lichen planus in humans. With this background of turmeric being effective in various inflammatory conditions and a need for a nontoxic agent to prevent radiation-induced mucositis, the present investigation was performed to assess whether turmeric was effective in reducing the severity of radiation-induced mucositis in patients undergoing radiation therapy for head and neck cancers

Patients and Methods

Patient Population

The subjects were histopathologically confirmed patients of head and neck cancer (according to TNM classification) scheduled to receive radiotherapy or chemoradiotherapy. Patients with recurrence of cancer in the oral cavity were eligible. Exclusion criteria included patients younger than 18 years, patients who were pregnant, patients who had oral surgery within the previous 6 weeks, received chemotherapy or radiation treatment previously to the head and neck region, patients using high doses of nonsteroidal anti-inflammatory drugs, patients with poor oral hygiene and xerostomia, and patients with comorbid conditions (poorly controlled diabetes mellitus, hypertension, schizophrenia, bipolar disorders, severe depression). The study was approved by the hospital ethical committee in accordance with the percepts established by the Helsinki Declaration. Patients and their caregivers indicated their willingness to participate in the study after the details of the study and the treatment involved had been explained to them. The subjects provided written informed consent and were also informed that they had the right to withdraw from the study at any time during the course of the study.

Study Design

This was a single-center, randomized, investigator-blinded clinical trial at the Mangalore Institute of Oncology and was conducted between January 2012 and September 2012. It was estimated that a minimum sample size of 40 subjects per treatment group would enable detection of clinically significant differences between treatment groups at a α level of .05 with a power of .80. At the start of the study, all participants were verified to

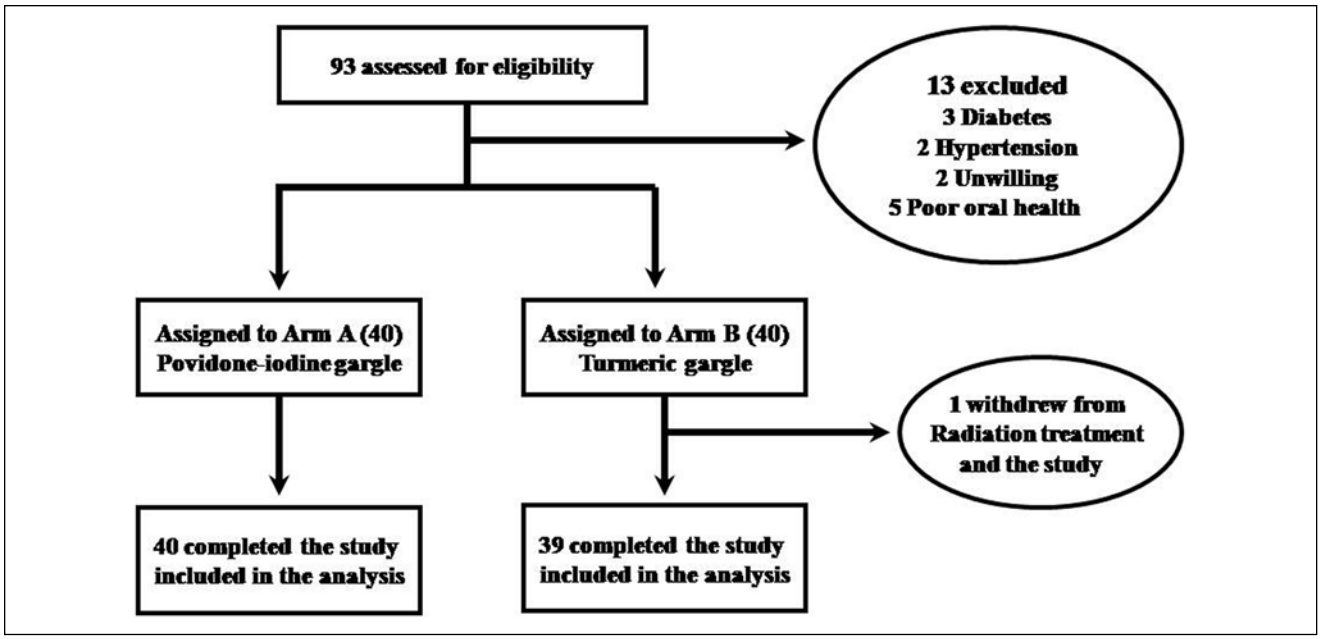

Figure 1. Patient flow in the randomized controlled study.

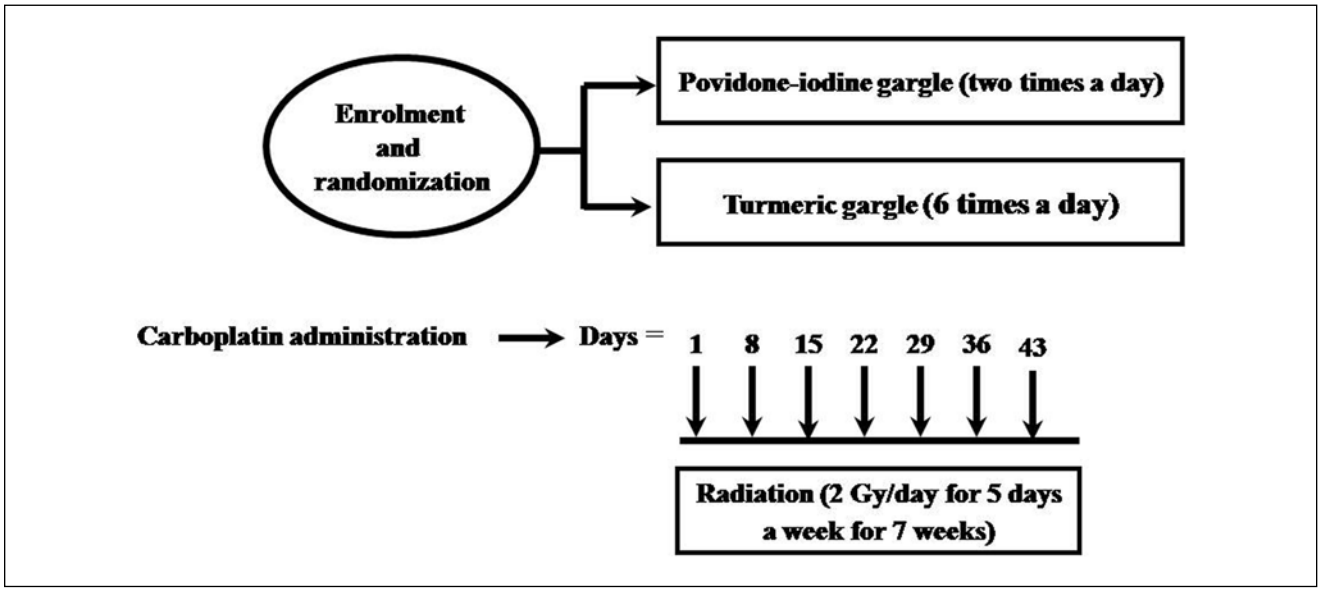

Figure 2. Schedule of chemoradiotherapy and oral treatment.

have no infected tooth, ulcers, or mucositis of the oral cavity. Of the eligible 93 patients, 84 satisfied the inclusion criteria and 80 agreed to participate in the study (Figure 1). The subjects were randomized using opaque envelopes to either povidone-iodine group (arm A) or turmeric (arm B). One of the authors oversaw the randomization. The sealed dark brown opaque envelopes (80 in total) used for randomization contained a card folded 4 times with the alphabet A or B (40 each) and were accordingly assorted to the respective arms.

All patients who participated in this study received external irradiation from a linear accelerator (Varian Medical systems, Unique 2012, Palo Alto, CA) at an average energy level of 6 MV. All planned fields were treated every day with no more than one fraction of 2 Gy per day, five times a week without any intended gaps for a planned target dose of 70 Gy (7 consecutive weeks). Whenever chemoirradiation was planned, carboplatin infusion (70 mg/m^2/day intravenous) was administered on a weekly basis 3 hours before exposure to the first weekly radiation[43] (Figure 2).

Standard oral, dental, medical, and supportive care was provided to all subjects of both cohorts by a qualified dental physician. The patients were also instructed to clean their teeth with a soft toothbrush 4 times a day. If spontaneous gum bleeding occurred they were instructed to only rinse with the study solutions and avoid aggravating the injury with toothbrush. A feeding tube was placed only when it was needed. Oral cavity smears for microbiological testing were carried out only in patient with clinical suspicion of a local infection and antimicrobials (antibiotics and antifungal agents) were administered only after culture sensitivity test. Additionally, rinsing with analgesic solutions was prescribed only if required. All patients were given dietary counseling and were recommended dietary supplements (protein enriched powders) to meet the nutritional requirements of the body.

Study Mouthwashes

Patients randomized to arm A used povidone-iodine solution diluted 1:100 (betadine 1 mL and 100 mL water; active comparator condition), while those randomized to arm B used turmeric. The patients of both the arms were trained by one of the authors to swish the oral cavity and expectorate in the presence of an attentive primary caregiver with instruction to adhere to the procedure as specified. They were also requested to swish after food and to abstain from eating for 30 minutes after use of mouthwash. The patients of the arm A were instructed to swish their mouth with 10 mL of the povidone-iodine mouthwash, twice a day (morning and night), for a period of 6 weeks as described by Madan et al.[44]

Turmeric solutions were suggested to be freshly prepared by dissolving the contents of standard turmeric powder (orangish yellow colored powder) available from the Himalaya Drug Company, Bangalore, India, in the form of capsules (batch no. L-AUS-133). The technical details of the turmeric powder are as follows (ash value 3.016% w/w, pH of 1% w/v solution in water 6.71, curcumin 2.42% w/w, lead 0.420 ppm, cadmium 0.030 ppm, arsenic 0.394 ppm, and mercury 0.283 ppm). In conventional Ayurvedic treatment, a paste of turmeric is made by grinding the dried roots and then boiled and cooled water and used for gargling to ameliorate ulcers of the mouth. In this study, we kept this principle in mind and adopted the procedure described above.

The caregivers were instructed to dissolve the contents of one turmeric capsule (400 mg) in approximately 80 mL of boiled and cooled water. The patients were instructed to swish their mouth with 10 mL of the turmeric solution for about 2 minutes and expectorate. The procedure was to be repeated 4 times at each time point and was to be performed for a total of 6 times in a day (1 hour prior to radiation, 1, 2, 4, and 6 hours after radiation, and once before going to bed) as indicated. During the course of the treatment, one of the investigators (CD) checked for the number of capsules being used on a weekly basis and repeatedly instructed the volunteers of both arms to adhere to the mouthwash instruction on every alternate day. The primary caregivers were also requested to monitor the volunteer's diet, medication when prescribed, oral hygiene, and skin care practices.

Outcome Measures

Mucositis was assessed before the start of the radiation treatment (during the mould preparation) and at weekly intervals during radiation therapy in accordance to the RTOG (Radiation Therapy Oncology Group) guidelines. The scale grades from 0 to 4, indicating progressively more severe degrees of oral mucositis.[2] Scores 1 and 2 were grouped as "tolerable mucositis" and scores 3 and 4 were termed "intolerable mucositis."[2] The observer recorded the grade of erythema or ulceration in upper and lower lips, right and left cheeks, right and left ventral and lateral tongue, floor of mouth, oropharynx, soft palate/fauces, and hard palate. A visiting orodental pathologist, unaware of the intervention received by the subjects, graded the mucosal reaction in the oral cavity using a battery-powered torchlight as described earlier.[2] The same observer also graded the mucositis in the inaccessible oropharnageal areas using the laryngoscope (Tele rigid telelaryngoscopy, model 8700CK, Karl Storz, Tuttlingen, Germany). As only one blinded researcher evaluated all the patients, calibration of assessors was not required and when differing grades of mucositis were present in the same oral cavity, the highest score was recorded as described earlier.[2]

Statistical Analysis

Analysis of variance was used to compare the extent of severe mucositis score on a weekly basis, testing equality of proportion for the delay in incidence and the number of tolerable and intolerable mucositis, while the χ^2 was used to compare the total incidence of worst-ever grades of ulceration, the number of treatment days lost due to intolerable mucositis and weight loss.

Results

Of the total 93 patients who reported to the Department of Radiation Oncology, Mangalore Institute of Oncology, Mangalore, India, during January 2012 to October 2012 for the treatment of head and neck malignancies, 80 patients, who fulfilled the inclusion/ exclusion criteria, participated in this trial and were randomly allocated into 1 of the 2 groups. The summary of the distribution of patients in the 2 groups based on age, sex, location of cancer, stage of cancer, treatment breaks, and difference in weight before and after the treatment is represented in Tables 1 and 2.

Table 1. Patient and Tumor Characteristics.

	Povidone-Iodine	Turmeric
Age in years	55.08 ± 13.14	56.8 ± 11.73
Gender		
Male	30	34
Female	10	6
Site		
Tongue	17	15
Buccal mucosa	4	5
Retromolar trigone	2	2
Palate	3	3
Pharynx (oro and hypo)	3	3
Alveolus	2	2
Cheek	1	0
Supraglottis	1	1
Lip	0	0
Pyriform sinus	1	1
Tonsil	4	3
Oral cavity	1	3
Vallecula	0	1
Vocal cord	1	1
TNM stage		
Primary		
T1	5	1
T2	16	19
T3	10	13
T4	7	7
TX	2	0
Regional nodes		
N0	9	14
N1	14	13
N2	3	2
N2a	3	5
N2b	2	2
N2c	6	3
N3	2	1
NX	1	0
Metastasis		
M0	30	27
MX	10	13

The study population consisted of 16 women and 64 men, whose age ranged from 26 to 85 years (mean 55.96 ± 12.25 years) and patients in both arms reported good treatment compliance. One patient in the turmeric group opted out of the planned cancer treatment after 34 Gy of radiation because of personal reasons. The remaining 39 patients in the turmeric and 40 of the povidone-iodine arm persisted with the planned treatment and also complied with the instructions on gargling, diet and dental care.

Radiation exposure caused mucositis in both the cohorts and the mean mucositis score is represented on a weekly basis in Figure 3. The onset of tolerable and intolerable mucositis was delayed in the patients using turmeric and testing equality of proportion showed a statistically significant difference between the groups throughout the study (Figures 4-6). Additionally, in the turmeric group, only 14 of 39 patients developed intolerable mucositis, while in the povidone-iodine group, 34 of the 40 patients developed intolerable mucositis and was significant ($P < 0.0001$; Table 2).

With respect to the number of treatment days lost, of the 39 patients in the turmeric arm, 7 (17.95%) experienced treatment interruption/delay caused by treatment reaction and all at the sixth or seventh week of radiation. The corresponding number for patients in the povidone-iodine arm was 9 (24%) of whom 5 needed treatment break at early stage (before 40 Gy; 4 weeks) and 4 toward the fifth to seventh week of the treatment after completing 40 Gy (Figure 6). The number of treatment days lost were 7.25 ± 0.56 and 7 ± 0.00 days, respectively, for povidone-iodine and turmeric group and was statistically not significant (Table 2). Additionally, it was also observed that when compared with the povidone-iodine (4.45 ± 2.15) group, the weight loss was less in the turmeric cohorts (3.92 ± 2.13) and was statistically significant ($P < 0.001$).

Discussion

Extensive research in the recent past has unequivocally shown that the kitchen spice turmeric and its principle compound curcumin possess myriad medicinal benefits and is of immense use especially in ameliorating inflammatory-mediated diseases and ailments of the gastrointestinal tract.[10-13] In the present study, exposure to ionizing radiation caused mucositis in both povidone-iodine and turmeric cohorts (Figure 2). However, in the participants using turmeric, the clinical appearance of mucositis was delayed and the intolerable mucositis was reduced, indicating turmeric to be effective in preventing mucositis.

Our results are similar to that of previous studies with honey, where various investigators have observed it to be effective in preventing against radiation-induced mucositis.[2,6,45-49] However, the apprehension that honey would enhance the radiation-related caries in cancer patients topically applying them during the course of the radiation[50,51] is a major concern as this would enhance dental caries and compromise the quality of life of the cancer survivors. In contrast, when compared with honey, turmeric may not have long-term adjunct effects as studies have shown it to be also beneficial in the treatment of various periodontal diseases.[40,52-54] Literature studies also show that turmeric possesses selective antineoplastic activity on neoplastic cells, chemopreventive effects, and antimetastatic activities,[14-23] all of which can be beneficial in the prevention of recurrence and distant spread of the cancer.

In cancer treatment, unplanned treatment interruptions and decrease in the planned treatment dose reduce the

Table 2. Treatment Characteristics.

	Povidone-Iodine	Turmeric	
Treatment			
Radiation only	10	8	
Chemo + radiation	16	15	
Surgery + chemo + radiation	14	17	
Dose of radiation	66.9 ± 0.54	65.7 ± 5.68^{NS}	
Breaks in treatment early (<4 weeks)	5/40	0/40	χ^2 test ($P < 0.01$)
Breaks in treatment after 4 weeks	4/40	7/39^{NS}	
Total number in treatment breaks	9/40	7/39^{NS}	
Number of days	7.25 ± 0.56	7 ± 0.00^{NS}	
Weight parameters (kg)			
Initial weight	52.82 ± 11.8	52.95 ± 11.4^{NS}	
Final weight	48.37 ± 11.48	49.02 ± 11.06^{NS}	
Percentage change in weight	4.45 ± 2.15	3.92 ± 2.13	ANOVA $P < 0.001$

Abbreviations: NS = not significant.

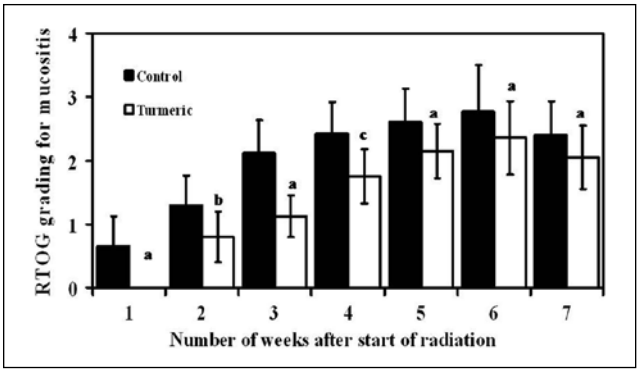

Figure 3. Graphical representation of the mucositis in the study groups through the radiation treatment period (analysis of variance: "a" indicates $P < 0.0001$; "b" indicates $P < 0.003$; "c" indicates $P < 0.001$).

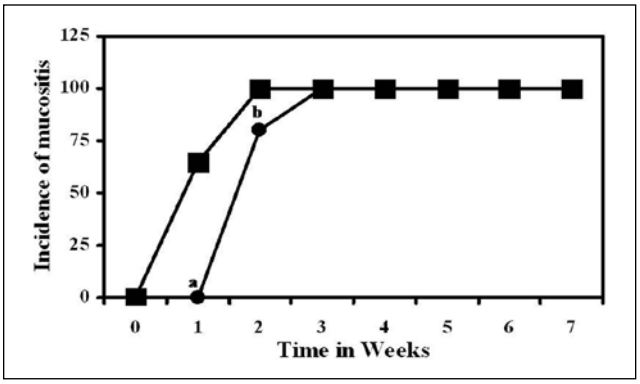

Figure 4. Graphical representation of the incidence of mucositis through the treatment period. Squares = povidone-iodine; circles = turmeric (testing of equality: "a" indicates $P < 0.0001$; "b" indicates $P < 0.001$).

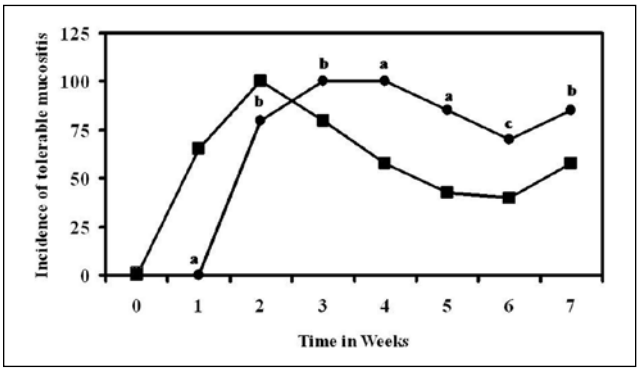

Figure 5. Graphical representation of the incidence of tolerable mucositis through the treatment period Squares = povidone-iodine; circle = turmeric (testing of equality "a" indicates $P < 0.0001$; "b" indicates $P < 0.001$; "c" indicates $P < 0.002$).

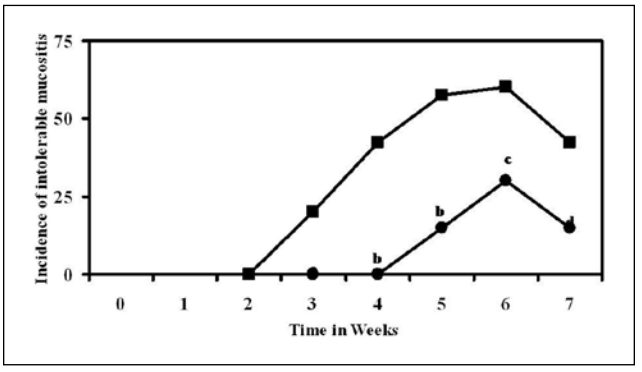

Figure 6. Graphical representation of the incidence of intolerable mucositis through the treatment period. Squares = povidone-iodine; circle = turmeric (testing of equality "a" indicates $P < 0.001$; "b" indicates $P < 0.0001$; "c" indicates $P < 0.004$; "d" indicates $P < 0.003$).

treatment efficacy, control of locoregional growth, and affect survival.[55] In this study, it was observed that when compared with the povidone-iodine arm, the cohort receiving turmeric had reduced treatment breaks and toward the end of the treatment schedule (5 weeks after the start of the treatment; Figure 3).The patients in the turmeric group were able to maintain better food intake because of reduced mucositis to the effect that the lower weight loss might have been due to better food consumption owing to reduced mucositis, although this was not measured specifically. Previous studies have shown that curcumin possesses anti-inflammatory[56,57] and antinociceptive effects[58,59] in relevant animal models of study, and it is quite possible that by reducing the inflammation and pain, turmeric might have contributed toward better dietary practice in these cohorts.

To the knowledge of the investigators, this is perhaps the first report to show the effectiveness of turmeric in preventing radiation-induced mucositis. However, literature does indicate that high dose of curcuminoids (6000 mg/d in 3 divided doses) was efficacious in controlling signs and symptoms of oral lichen planus and to also reduce erythema, ulceration, and total modified oral mucositis index scores.[42] Additionally, preclinical studies with laboratory rats have also shown that a formulation containing curcumin, α-tocopherol, and sunflower oil was effective in preventing radiation-induced oral mucositis.[60] Together, these observations clearly indicate the usefulness of turmeric in preventing mucositis and substantiate our observations.

The process of mucositis is complex and includes initiation, upregulation, and generation of messenger signals, signaling and amplification, ulceration, and healing stage.[1] At a cellular level, exposure to ionizing radiation causes generation of free radicals (reactive oxygen species and reactive nitrogen species),[1] DNA strand breaks and to activate transcription factors (NF-κB).[1] Additionally, the immune cells also produce pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1 [IL-1], IL-6), which exacerbate the tissue injury and cell death.[1,61,62] Numerous studies in the past with various experimental models have equivocally shown that turmeric/curcumin possess free radical scavenging effects on both reactive oxygen species and reactive nitrogen species, to reduce the levels of pro-inflammatory cytokines and NF-κB[11-13] and triggering of these mechanisms could have contributed toward the observed protection in the study.

In addition to the cellular inflammatory effects, the denuded epithelium may also provide access to the oral microbial flora and this may contribute to the underlying pathogenesis and exacerbate the condition.[63] Turmeric/curcumin has also been reported to possess antimicrobial effects, including against the clinically relevant methicillin-resistant *Staphylococcus aureus* strains[64] With regard to the bacteria involved in the process of oral mucositis, in vitro studies with *Moraxella catarrhali*, a facultative upper respiratory tract pathogen have shown that curcumin possess bactericidal effects to inhibit bacterial adherence and invasion to Detroit 562 (pharyngeal cells) and to reduce Mcat-induced pro-inflammatory activation by suppressing release of pro-inflammatory cytokine IL-8.[65] Pre-incubation of Detroit cells with 200 μM curcumin for 5 to 60 minutes resulted in complete suppression of the release of tumor necrosis factor-α, IL-6, IL-8, monocyte chemoattractant protein 1, granulocyte macrophage-colony stimulating factor, and vascular endothelial growth factor.[65] Additionally, the investigators have also observed that repetitive exposure to curcumin caused recurring suppression of cytokine/chemokine expression.[65]

Turmeric has been used as a wound healing agent for centuries[32-35] and animal studies have shown that when compared with untreated controls, the application of curcumin enhances faster wound closure of punch wounds in curcumin-treated animals.[37] Histopathological observations indicate that in the cohorts where turmeric was applied, increased levels of reepithelialization of epidermis; migration of myofibroblasts, fibroblasts, and macrophages to the wound bed; promotion of neovascularization and greater deposition of collagen was pronounced and that this effect was mediated by increased levels of transforming growth factor-β1.[37] Additionally, studies have also shown that turmeric and its principal compound curcumin possess anti-inflammatory[66] effects, promote reepithelialization,[67] and enhance healing of wounds created in skin exposed to radiation.[36-39] In lieu of all these observations it can be postulated that the beneficial effects of turmeric in preventing radiation-induced mucositis can be best explained by its anti-inflammatory, antioxidant, antimicrobial, modulating cytokines, and by enhancing wound healing process.

Summary and Conclusion

The notable observation of this study is that turmeric was effective in preventing/reducing radiation-induced mucositis and that the effect was better than the standard povidone-iodine used as an active comparator. In our study, the patients in arm A rinsed only twice per day with povidone-iodine solution, while the patients in arm B swished with turmeric solution 6 times a day. This schedule of 6 times a day for the turmeric cohorts was adopted on recommendation of senior Ayurvedic physicians, who recommend similar protocol of treatment for treating oral ulcers while that for the povidone-iodine described by Madan et al[44] is a widely used protocol locally in Mangalore. It is quite possible that this increase in swish in arm B might have also contributed to the observed protection and needs to be validated with different number of swishes with turmeric solution. The use of active placebo (water only) was avoided on ethical grounds and to avoid the risk of developing any mucositis and associated oral complications. The second

important aspect that merits further study is that the study arm assigned to turmeric intervention was not blinded to the patients. Turmeric has distinctive organoleptic properties and has been used regularly as a culinary and therapeutic agent for centuries in Asia. It is quite possible that the psychological influence of turmeric's beneficial effects may have also had played a role in the therapeutic effects observed in the turmeric cohorts and needs to be validated in future studies with exactly matching nontoxic control and including the pain scale and quality of life assessment through questioners/interviews. As far as the authors are aware, only metanil yellow resembles turmeric powder. However, the use of this chemical was not considered because of its toxicity profile. Turmeric has an excellent safety profile and wide acceptability. Within the authors' admitted limitations, it can be concluded that turmeric has a significant effect in delaying and reducing radiation-induced mucositis. As a conclusion, our study shows for the first time that regular turmeric swish is effective in preventing the radiation-induced acute mucosal inflammation and could be of immense use in clinics when the existing lacunae are bridged.

Acknowledgments

The authors are extremely grateful to Dr Prahlad Patki and Dr Rafique of Himalaya Drug Company of Bangalore for providing the necessary information on turmeric.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Sonis ST, Elting LS, Keefe D, et al. Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 suppl):1995-2025.
2. Khanal B, Baliga M, Uppal N. Effect of topical honey on limitation of radiation-induced oral mucositis: an intervention study. *Int J Oral Maxillofac Surg*. 2010;39: 1181-1185.
3. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. *Int J Radiat Oncol Biol Phys*. 2007;68:1110-1120.
4. Peterman A, Cella D, Glandon G, Dobrez D, Yount S. Mucositis in head and neck cancer: economic and quality-of-life outcomes. *J Natl Cancer Inst Monogr*. 2001;29:45-51.
5. Rodríguez-Caballero A, Torres-Lagares D, Robles-García M, Pachón-Ibáñez J, González-Padilla D, Gutiérrez-Pérez JL. Cancer treatment-induced oral mucositis: a critical review. *Int J Oral Maxillofac Surg*. 2012;41:225-238.
6. Biswal BM, Zakaria A, Ahmad NM. Topical application of honey in the management of radiation mucositis: a preliminary study. *Support Care Cancer*. 2003;11:242-248.
7. You WC, Hsieh CC, Huang JT. Effect of extracts from indigowood root (*Isatis indigotica Fort*.) on immune responses in radiation-induced mucositis. *J Altern Complement Med*. 2009;15:771-778.
8. Maddocks-Jennings W, Wilkinson JM, Cavanagh HM, Shillington D. Evaluating the effects of the essential oils *Leptospermum scoparium* (manuka) and *Kunzea ericoides* (kanuka) on radiotherapy induced mucositis: a randomized, placebo controlled feasibility study. *Eur J Oncol Nurs*. 2009;13:87-93.
9. Das D, Agarwal SK, Chandola HM. Protective effect of Yashtimadhu (*Glycyrrhiza glabra*) against side effects of radiation/chemotherapy in head and neck malignancies. *Ayu*. 2011;32:196-199.
10. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (*Curcuma longa*). *J Altern Complement Med*. 2003;9:161-168.
11. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK.Turmeric and curcumin: biological actions and medicinal applications. *Curr Sci*. 2004;87:44-53.
12. Calabrese V, Bates TE, Mancuso C, et al. Curcumin and the cellular stress response in free radical-related diseases. *Mol Nutr Food Res*. 2008;52:1062-1073.
13. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J*. 2013;15:195-218.
14. Azuine MA, Bhide SV. Adjuvant chemoprevention of experimental cancer: catechin and dietary turmeric in forestomach and oral cancer models. *J Ethnopharmacol*. 1994;44:211-217.
15. Li N, Chen X, Han C, Chen J. Chemopreventive effect of tea and curcumin on DMBA-induced oral carcinogenesis in hamsters [in Chinese]. *Wei Sheng Yan Jiu*. 2002;31:354-357.
16. Li N, Chen X, Liao J, et al. Inhibition of 7,12-dimethylbenz[a] anthracene (DMBA) -induced oral carcinogenesis in hamsters by tea and curcumin. *Carcinogenesis*. 2002;23:1307-1313.
17. Manoharan S, Balakrishnan S, Menon VP, Alias LM, Reena AR. Chemopreventive efficacy of curcumin and piperine during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Singapore Med J*. 2009;50:139-146.
18. Zhang XY, Chen XF, Sun Z, Miao CC, Ge LH, Tian ZC. Chemopreventive effect of boswellic acid and curcumin on 7,12-dimethyl benzanthracene-induced hamster cheek pouch carcinogenesis [in Chinese]. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2011;46:678-683.
19. Ip SW, Wu SY, Yu CC, et al. Induction of apoptotic death by curcumin in human tongue squamous cell carcinoma SCC-4 cells is mediated through endoplasmic reticulum stress and mitochondria-dependent pathways. *Cell Biochem Funct*. 2011;29:641-650.
20. Sharma C, Kaur J, Shishodia S, Aggarwal BB, Ralhan R. Curcumin down regulates smokeless tobacco-induced NF-κB

activation and COX-2 expression in human oral premalignant and cancer cells. *Toxicology*. 2006;228:1-15.
21. Atsumi T, Tonosaki K, Fujisawa S. Induction of early apoptosis and ROS-generation activity in human gingival fibroblasts (HGF) and human submandibular gland carcinoma (HSG) cells treated with curcumin. *Arch Oral Biol*. 2006;51: 913-921.
22. Dujic J, Kippenberger S, Ramirez-Bosca A, et al. Curcumin in combination with visible light inhibits tumor growth in a xenograft tumor model. *Int J Cancer*. 2009;124:1422-1428.
23. Liao S, Xia J, Chen Z, et al. Inhibitory effect of curcumin on oral carcinoma CAL-27 cells via suppression of Notch-1 and NF-κB signaling pathways. *J Cell Biochem*. 2011;112:1055-1065.
24. Antunes LM, Darin JD, Bianchi Nde L. Effects of the antioxidants curcumin or selenium on cisplatin-induced nephrotoxicity and lipid peroxidation in rats. *Pharmacol Res*. 2001;43:145-150.
25. Ilbey YO, Ozbek E, Cekmen M, Simsek A, Otunctemur A, Somay A. Protective effect of curcumin in cisplatin-induced oxidative injury in rat testis: mitogen-activated protein kinase and nuclear factor-kappa B signaling pathways. *Hum Reprod*. 2009;24:1717-1725.
26. Kuhad A, Pilkhwal S, Sharma S, Tirkey N, Chopra K. Effect of curcumin on inflammation and oxidative stress in cisplatin-induced experimental nephrotoxicity. *J Agric Food Chem*. 2007;55:10150-10155.
27. Alaikov T, Konstantinov SM, Tzanova T, Dinev K, Topashka-Ancheva M, Berger MR. Antineoplastic and anticlastogenic properties of curcumin. *Ann N Y Acad Sci*. 2007;1095: 355-370.
28. Chan WH, Wu CC, Yu JS. Curcumin inhibits UV irradiation-induced oxidative stress and apoptotic biochemical changes in human epidermoid carcinoma A431 cells. *J Cell Biochem*. 2003;90:327-338.
29. Agrawal R, Kaur IP. Inhibitory effect of encapsulated curcumin on ultraviolet-induced photoaging in mice. *Rejuvenation Res*. 2010;13:397-410.
30. Srinivasan M, Sudheer AR, Pillai KR, Kumar PR, Sudhakaran PR, Menon VP. Modulatory effects of curcumin on γ-radiation-induced cellular damage in primary culture of isolated rat hepatocytes. *Environ Toxicol Pharmacol*. 2007;24:98-105.
31. Nada AS, Hawas AM, Amin Nel-D, Elnashar MM, Abd Elmageed ZY. Radioprotective effect of *Curcuma longa* extract on γ-irradiation-induced oxidative stress in rats. *Can J Physiol Pharmacol*. 2012;90:415-423.
32. Sidhu GS, Singh AK, Thaloor D, et al. Enhancement of wound healing by curcumin in animals. *Wound Repair Regen*. 1998;6:167-177.
33. Panchatcharam M, Miriyala S, Gayathri VS, Suguna L. Curcumin improves wound healing by modulating collagen and decreasing reactive oxygen species. *Mol Cell Biochem*. 2006;290:87-96.
34. Singer AJ, McClain SA, Romanov A, Rooney J, Zimmerman T. Curcumin reduces burn progression in rats. *Acad Emerg Med*. 2007;14:1125-1129.
35. Rao MC, Sudheendra AT, Nayak PG, Paul P, Kutty GN, Shenoy RR. Effect of dehydrozingerone, a half analog of curcumin on dexamethasone-delayed wound healing in albino rats. *Mol Cell Biochem*. 2011;355:249-256.
36. Jagetia GC, Rajanikant GK. Effect of curcumin on radiation-impaired healing of excisional wounds in mice. *J Wound Care*. 2004;13:107-109.
37. Jagetia GC, Rajanikant GK. Role of curcumin, a naturally occurring phenolic compound of turmeric in accelerating the repair of excision wound, in mice whole-body exposed to various doses of gamma-radiation. *J Surg Res*. 2004;120: 127-138.
38. Jagetia GC, Rajanikant GK. Curcumin treatment enhances the repair and regeneration of wounds in mice exposed to hemibody gamma-irradiation. *Plast Reconstr Surg*. 2005;115: 515-528.
39. Jagetia GC, Rajanikant GK. Acceleration of wound repair by curcumin in the excision wound of mice exposed to different doses of fractionated γ-radiation. *Int Wound J*. 2012;9:76-92.
40. Mali AM, Behal R, Gilda SS. Comparative evaluation of 0.1% turmeric mouthwash with 0.2% chlorhexidine gluconate in prevention of plaque and gingivitis: a clinical and microbiological study. *J Indian Soc Periodontol*. 2012;16:386-391.
41. Hastak K, Lubri N, Jakhi SD, et al. Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis. *Cancer Lett*. 1997;116: 265-269.
42. Chainani-Wu N, Madden E, Lozada-Nur F, Silverman S Jr. High-dose curcuminoids are efficacious in the reduction in symptoms and signs of oral lichen planus. *J Am Acad Dermatol*. 2012;66:752-760.
43. Pazdur R, Wagman LD, Camphausen K, & Hoskins WJ. eds. *Cancer Management: A Multidisciplinary Approach. Medical, Surgical, and Radiation Oncology*. 12th ed. Norwalk, CT: CMP Healthcare Media; 2009.
44. Madan PD, Sequeira PS, Shenoy K, Shetty J. The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: a randomized control trial. *J Cancer Res Ther*. 2008;4:3-8.
45. Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, Omidi S. The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial. *J Contemp Dent Pract*. 2008;9:40-47.
46. Rashad UM, Al-Gezawy SM, El-Gezawy E, Azzaz AN. Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer. *J Laryngol Otol*. 2009;123:223-228.
47. Bardy J, Molassiotis A, Ryder WD, et al. A double-blind, placebo-controlled, randomised trial of active manuka honey and standard oral care for radiation-induced oral mucositis. *Br J Oral Maxillofac Surg*. 2012;50:221-226.
48. Jayachandran S, Balaji N. Evaluating the effectiveness of topical application of natural honey and benzydamine hydrochloride in the management of radiation mucositis. *Indian J Palliat Care*. 2012;18:190-195.
49. Maiti PK, Ray A, Mitra TN, Jana U, Bhattacharya J, Ganguly S. The effect of honey on mucositis induced by chemo-radiation in head and neck cancer. *J Indian Med Assoc*. 2012;110:453-456.

50. Van den Wyngaert T. Topical honey application to reduce radiation-induced oral mucositis: a therapy too sweet to ignore? *J Evid Based Dent Pract*. 2012;12:203-205.
51. Santos-Silva AR, Rosa GB, Eduardo CP, Dias RB, Brandao TB. Increased risk for radiation-related caries in cancer patients using topical honey for the prevention of oral mucositis. *Int J Oral Maxillof Surg*. 2011;40:1335-1336.
52. Waghmare PF, Chaudhari AU, Karhadkar VM, Jamkhande AS. Comparative evaluation of turmeric and chlorhexidine gluconate mouthwash in prevention of plaque formation and gingivitis: a clinical and microbiological study. *J Contemp Dent Pract*. 2011;12:221-224.
53. Nagpal M, Sood S. Role of curcumin in systemic and oral health: an overview. *J Nat Sci Biol Med*. 2013;4:3-7.
54. Chaturvedi TP. Uses of turmeric in dentistry: an update. *Indian J Dent Res*. 2009;20:107-109.
55. Rosenthal DI. Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes. *J Support Oncol*. 2007;5(9 suppl 4):23-31.
56. Conney AH, Lysz T, Ferraro T, et al. Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metabolism in mouse skin. *Adv Enzyme Regul*. 1991;31:385-396.
57. Graf J. Herbal anti-inflammatory agents for skin disease. *Skin Ther Lett*. 2000;5:3-5.
58. Sharma S, Kulkarni SK, Agrewala JN, Chopra K. Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. *Eur J Pharmacol*. 2006;536:256-261.
59. Zhao X, Xu Y, Zhao Q, Chen CR, Liu AM, Huang ZL. Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: descending monoamine system and opioid receptors are differentially involved. *Neuropharmacology*. 2012;62:843-854.
60. Rezvani M, Ross GA. Modification of radiation-induced acute oral mucositis in the rat. *Int J Radiat Biol*. 2004;80:177-182.
61. Gibson RJ, Bowen JM, Cummins AG, Logan R, Healey T, Keefe DM. Ultrastructural changes occur early within the oral mucosa following cancer chemotherapy. *Support Care Cancer*. 2004;12:389.
62. Logan RM, Gibson RJ, Sonis ST, Keefe DM. Nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX-2) expression in the oral mucosa following cancer chemotherapy. *Oral Oncol*. 2007;43:395-401.
63. Raber-Durlacher JE, Elad S, Barasch A. Oral mucositis. *Oral Oncol*. 2010;46:452-456.
64. Kim KJ, Yu HH, Cha JD, Seo SJ, Choi NY, You YO. Antibacterial activity of *Curcuma longa* L. against methicillin-resistant *Staphylococcus aureus. Phytother Res*. 2005;19:599-604.
65. Lüer S, Troller R, Jetter M, Spaniol V, Aebi C. Topical curcumin can inhibit deleterious effects of upper respiratory tract bacteria on human oropharyngeal cells in vitro: potential role for patients with cancer therapy induced mucositis? *Support Care Cancer*. 2011;19:799-806.
66. Lüer S, Troller R, Aebi C. Antibacterial and anti-inflammatory kinetics of curcumin as a potential antimucositis agent in cancer patients. *Nutr Cancer*. 2012;64:975-981.
67. López-Jornet P, Camacho-Alonso F, Jiménez-Torres MJ, Orduña-Domingo A, Gómez-García F. Topical curcumin for the healing of carbon dioxide laser skin wounds in mice. *Photomed Laser Surg*. 2011;29:809-814.