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Role of turmeric extract in minimising mucositis in patients receiving radiotherapy for head and neck squamous cell cancer: a randomised, placebo-controlled trial

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Abstract

Objective. To determine the role of turmeric extract in reducing mucositis in patients undergoing radiotherapy for head and neck cancer.

Methods. Sixty-one patients who underwent radiotherapy were included in the study and randomised into groups A and B. Patients in group A received 500 mg of turmeric extract (BCM-95) thrice daily, while patients in group B received placebo until radiotherapy completion. All patients were assessed for oral mucositis on a weekly basis during treatment and two months post-treatment using the National Cancer Institute Common Terminology Criteria for Adverse Events and World Health Organization criteria.

Results. Both groups had a similar grade of mucositis in first two weeks of treatment. The severity of mucositis was progressive in the control group, with four patients developing grade 3 mucositis by week four. In group A, however, the majority of patients (73.3 per cent) had grade 1 mucositis after four weeks of treatment. The difference was statistically significant from the third week onwards ($p < 0.001$).

Conclusion. Turmeric extract reduces the incidence and severity of radiation-induced mucositis, which can benefit patients undergoing radiation for head and neck cancer.

Main Article

Dr P Arun takes responsibility for the integrity of the content of the paper

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Introduction

Head and neck squamous cell carcinoma (SCC) is one of the commonest malignancies in the Indian population, and it accounts for 12 per cent of all cancers in India.[1] Various treatment modalities are used for SCC of head and neck region, including surgery, radiotherapy and chemotherapy, which can be used singly or in combination. Each modality of treatment gives rise to various complications, which at times leads to treatment discontinuation. Radiotherapy and chemotherapy may be required post-operatively, depending on the tumour stage, the resection margins, perineural or vascular invasion, and nodal status. These form the main modalities of treatment in inoperable patients and are known to affect tumour response through various mechanisms.[2,3]

One of the dose-limiting factors in patients undergoing radiation is radiation-induced mucositis, which can result in treatment discontinuation. Various possible treatments for this have been investigated, ranging from locally applied agents, such as vitamin A, vitamin E, L-glutamine, local anaesthetics, topical corticosteroids, chlorhexidine and povidone-iodine mouthwashes, to systemic agents such as cyclooxygenase-2 inhibitors, N-acetylcysteine, colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, transforming growth factor-β3, analgesics, azelastine, systemic corticosteroids, antibacterial agents, and antiviral agents. Despite the range of potential treatments available, no single agent has been approved by the US Food and Drug Administration for the treatment of radiation-induced mucositis.[4]

Curcumin, demethoxycurcumin and bisdemethoxycurcumin, collectively known as curcuminoids, constitute the biologically active constituents of *Curcuma longa* L or turmeric.[5] Poor oral bioavailability limits the beneficial action of curcumin.[6] The combination of curcuminoids and essential oil of turmeric can enhance the oral bioavailability of curcumin,[7] and has been found to be absolutely safe.[8] Bioenhanced curcumin was studied in a carrageenan-induced acute inflammatory model in Wistar rats and showed significant anti-inflammatory activity.[9]

Turmeric extract has long been known to be an anti-inflammatory agent. Thus, it may hold promise in limiting radiation-induced mucositis. It is therefore an ideal drug to try in patients with head and neck cancer undergoing radiotherapy or concurrent chemoradiation.

Materials and methods

A randomised, single-blinded clinical study was conducted in the Department of Otorhinolaryngology and Head and Neck Surgery of the R L Jalappa Hospital and

Research Centre, Kolar, India, for which all eligible patients from December 2012 to June 2014 were evaluated. Written informed consent was obtained from all patients. Ethical committee clearance was obtained from the institution before the study was initiated. The study was carried out under the principles of the International Conference on Harmonisation Good Clinical Practice ethical guidelines outlined in the Helsinki Declaration of 1975, as revised in 2008. The investigation was registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN13817594).

All adult patients undergoing post-operative radiotherapy, post-operative chemoradiotherapy or concurrent chemoradiotherapy for advanced head and neck SCC were included in the study. Patients with non-squamous head and neck cancer, severe acid peptic disease, distant metastasis or recurrent tumours were excluded, as were those who did not give consent for the treatment or defaulted on treatment.

A detailed clinical examination was carried out. Patients were staged according to the American Joint Committee on Cancer 2012 tumour–node–metastasis (TNM) classification. All patients underwent biopsy for histopathological diagnosis. Other required tests were conducted, including complete blood investigations (e.g. liver and renal function tests), X-ray scans of the mandible and chest, contrast-enhanced computed tomography, and electrocardiography.

All patients enrolled in the study were randomised into groups using a 4×4 block randomisation sequence generated by an independent statistician. In this method, four sets were created, and then random numbers were generated from 1 to 4 using Research Randomiser (a free online resource), as shown in Figure 1. The patients were subsequently randomised into one of two groups: a study group (group A) and a control group (group B). The investigator assigned the participants into the study using a serially numbered random list; the allocation was concealed using sequentially numbered containers. This was a single-blinded study: only the participants were blinded to the intervention.

Patients in group A received a daily dose of 500 mg of turmeric extract capsules (BCM-95®/Curcugreen®) thrice daily (total dose of 1.5 g/day) and were asked to take the capsules after food. Patients in group B received placebo capsules thrice daily. The patients started taking the capsules on the first day of radiation and continued until the completion of radiotherapy.

Sample size calculation was performed using R software, version 3.6. Based on a power of 80 per cent and a type 1 error of alpha of 0.05, a sample size of 30 participants per group was found sufficient for this study.

The turmeric extract used in this study was a formulation of curcuminoids and essential oils of turmeric (BCM-95®). The turmeric raw material was identified by a qualified botanist and a skip-lot analysis was conducted to authenticate the raw material for extraction. The herbal product used in the study was processed from the dried rhizome of turmeric (*Curcuma longa* L (Zingiberaceae)) and manufactured by Arjuna Natural, Aluva, India. The raw material to extract ratio was 25:1, and 100 per cent ethyl acetate was used as the extraction solvent.

Each 500 mg capsule of turmeric extract contained not less than 95 per cent of total curcuminoids and essential oil complex (curcumin, demethoxycurcumin, bisdemethoxycurcumin and volatile oils from turmeric rhizome), with curcuminoids not less than 88 per cent and curcumin not less than 68 per cent, as analysed using high-performance liquid chromatography. Heavy metals were analysed using inductively coupled plasma mass spectrometry and found to be less than 10 parts per million, and the residual solvent content met the United States Pharmacopeia requirements. The microbial content was analysed using Association of Official Agricultural Chemists and Bacteriological Analytical Manual methods, and was found to be within acceptable limits.

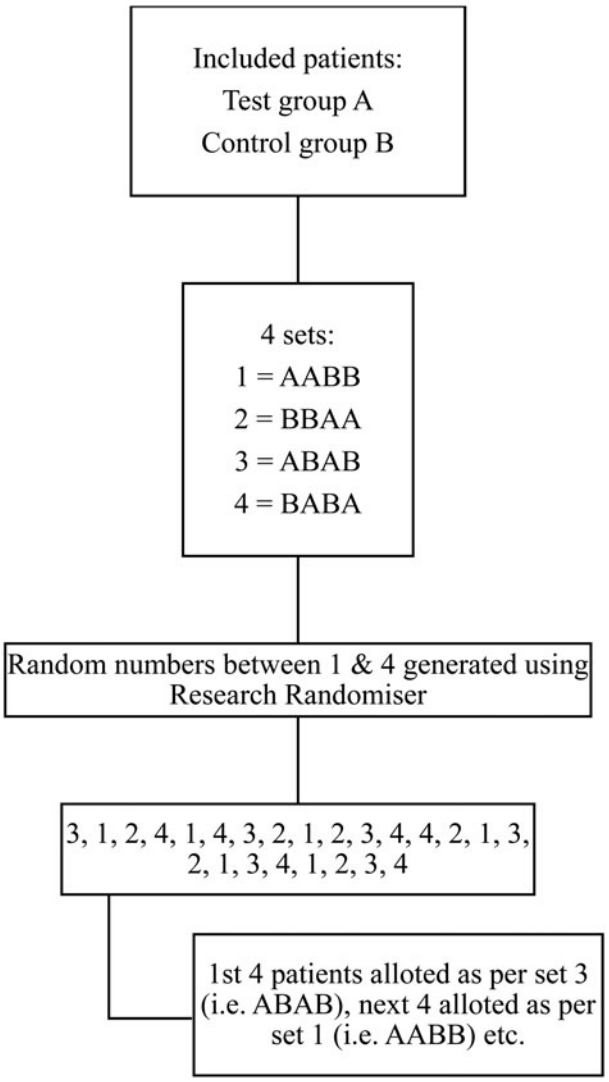

Fig. 1. Study randomisation procedure.

The herbal product comes under the category of nutraceuticals. It has been approved by the Food Safety and Standards Authority of India, and has been given a 'generally recognised as safe' designation by the US Food and Drug Administration.

The placebo capsule contained starch powder. Both types of capsule were identical in colour and shape. Voucher specimens of the raw material, and retention samples of the herbal extract and placebo, have been kept in the research and development laboratory for future reference.

A total of 64 patients were included in the study, and all of them received external beam radiotherapy using the isotope cobalt 60. Three patients were excluded from the study as they defaulted the treatment. Sixty-one patients completed the study. The demographic profile of the patients included in the study and their habit profile are shown in Table 1 and Figure 2 respectively. The primary tumour site and TNM staging are shown in Table 2.

All patients received one fraction (2 Gy) of radiotherapy per day, five times a week, for a total dose of 66 Gy; the spinal cord

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Table 1. Age and sex distribution

	Sex		Age group (years)					
Group	Male	Female	30–40	41–50	51–60	61–70	71–80	81–90
Group A	50	50	23.3	16.6	23.3	33.3	3.3	0
Group B	41.9	58.1	25.8	32.2	12.9	18.7	6.4	3.2

Data represent percentages of patients. Group A = turmeric extract (study) group ($n = 30$); group B = placebo (control) group ($n = 31$).

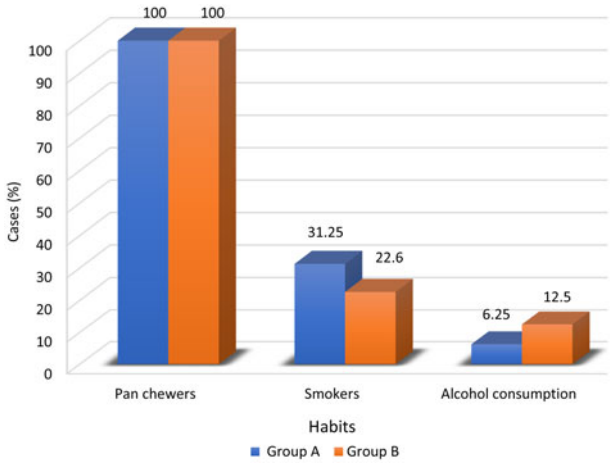

Fig. 2. Habit profile of patients included in the study.

Table 2. Site and stage of primary tumour

Primary tumour characteristic	Group A	Group B
Primary tumour site		
– Oral cavity	73.3	83.9
– Oropharynx	16.7	9.7
– Glottis	6.7	3.2
– Supraglottis	3.3	3.2
Primary tumour stage		
– Stage II	0	3.2
– Stage III	20	32.2
– Stage IVa	73.3	61.3
– Stage IVb	0	3.2

Data represent percentages of patients. Group A = turmeric extract (study) group ($n = 30$); group B = placebo (control) group ($n = 31$).

was excluded after 46 Gy. Patients scheduled for chemoradiation received cisplatin infusion (50 mg/m^2) weekly, along with radiotherapy.

The subjects remained as in-patients during their entire course of treatment. Dental and medical parameters were checked regularly, and supportive care was given to subjects in both groups. Patients were asked to maintain good oral hygiene. The treatments undertaken by the patients are shown in Table 3.

All 61 patients included were assessed for mucositis weekly during treatment and two months after treatment, using subjective and objective scales. The subjective scale used for assessment was the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The objective scale used was the World Health Organization scale for oral mucositis.[10] These scales are described in Table 4.

Table 3. Primary modality of treatment

Primary modality of treatment	Group A	Group B
Surgery + RT	53.3	64.5
RT + chemotherapy	40	29.1
Surgery + RT + chemotherapy	6.7	6.4

Data represent percentages of patients. Group A = turmeric extract (study) group ($n = 30$); group B = placebo (control) group ($n = 31$). RT = radiotherapy

IBM SPSS® software (version 24) was used to perform the statistical analysis. The chi-square test was used to compare the categorical data of study groups. *P*-values of less than or equal to 0.05 were considered statistically significant.

Results

Both groups had similar grades of mucositis in the first two weeks of treatment. There were no statistical differences between the two groups for either the objective or subjective scales, as shown in Table 5. However, from the third week onwards, patients in group A (turmeric extract (study) group; total $n = 30$) showed decreases in the incidence and severity of mucositis, compared to group B (placebo (control) group; total $n = 31$) (Table 5). After three weeks of treatment, in group B, 6.4 per cent of patients ($n = 2$) had grade 3 mucositis and 71 per cent ($n = 22$) had progressed to grade 2 mucositis. In group A, however, only 10 per cent of patients ($n = 3$) had grade 2 mucositis; the majority of patients (86.7 per cent; $n = 26$) had only grade 1 mucositis (Table 5). The difference between the groups was statistically significant ($p < 0.001$).

At the end of the fourth week of treatment, 4 patients (13 per cent) in group B had grade 3 mucositis and 21 (68 per cent) had grade 2 mucositis. In comparison, in group A, none of the patients had grade 3 mucositis and 22 patients (73.3 per cent) had grade 1 mucositis, as shown in Table 5. The difference was found to be statistically significant ($p < 0.001$). At follow up, two months after treatment, 24 patients (77.5 per cent) had persistent grade 2 mucositis in group B, whereas only 2 patients (6.7 per cent) had grade 2 mucositis in group A. In group A, most patients (86.6 per cent; $n = 26$) had only grade 1 mucositis, as shown in Table 5. The difference was found to be statistically significant ($p < 0.001$). The subjective scale assessment of mucositis showed a similar picture to objective scale results, as shown in Table 5.

Discussion

Multimodality treatment, using a combination of surgery, radiation and chemotherapy, has become the preferred treatment for head and neck SCC, more so in advanced tumours.

Studies have shown turmeric extract to be highly pleiotropic. It is known to interact on various molecular levels of

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Table 4. Objective and subjective scales used for mucositis assessment

Scale	Grade	Description
Objective WHO oral mucositis scale	Grade 0	No oral mucositis
	Grade 1	Erythema & soreness
	Grade 2	Ulcers, able to eat solids
	Grade 3	Ulcers, requires liquid diet (because of mucositis)
	Grade 4	Ulcers, alimentation not possible (because of mucositis)
Subjective NCI CTCAE assessment, version 4.0	Grade 1	Asymptomatic or mild symptoms; intervention not indicated
	Grade 2	Moderate pain, not interfering with oral intake; modified diet indicated
	Grade 3	Severe pain, interfering with oral intake
	Grade 4	Life-threatening consequences; urgent intervention indicated
	Grade 5	Death

WHO = World Health Organization; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Table 5. Objective and subjective mucositis assessment results

Scale	Group	Parameter	Week 1	Week 2	Week 3	Week 4	2 months' follow up
Objective scale		*P*-value	0.488	0.171	0.001	0.001	0.001
	Group A	Grade 0	96.7	43.3	3.3	6.7	6.7
		Grade 1	3.3	53.3	86.7	73.3	86.6
		Grade 2	0	3.3	10	20	6.7
		Grade 3	0	0	0	0	0
		Grade 4	0	0	0	0	0
	Group B	Grade 0	93.6	19.4	0	0	0
		Grade 1	6.4	74.2	22.6	19.3	19.3
		Grade 2	0	6.4	71	67.7	77.5
		Grade 3	0	0	6.4	12.9	3.2
		Grade 4	0	0	0	0	0
Subjective scale		*P*-value	0.488	0.171	0.001	0.001	0.001
	Group A	Grade 1	96.7	43.3	3.3	3.3	3.3
		Grade 2	3.3	53.3	83.3	76.7	90
		Grade 3	0	3.3	13.3	20	6.7
		Grade 4	0	0	0	0	0
		Grade 5	0	0	0	0	0
	Group B	Grade 1	93.6	19.4	0	0	0
		Grade 2	6.4	74.2	22.6	19.3	19.3
		Grade 3	0	6.4	71	67.7	77.5
		Grade 4	0	0	6.4	12.9	3.2
		Grade 5	0	0	0	0	0

Data represent percentages of patients with each grade at each time point, unless indicated otherwise. Group A = turmeric extract (study) group ($n = 30$); group B = placebo (control) group ($n = 31$).

inflammation. Curcumin modulates its anti-inflammatory action by: down-regulating the activity of cyclo-oxygenase-2, lipoxygenase and inducible nitric oxide synthase enzymes, by inhibiting nuclear factor kappa B (NFκB) transcription factor; and via the production of inflammatory cytokines like tumour necrosis factor-α, interleukins 1, 2, 6, 8 and 12, monocyte chemotactic protein-1, and monocyte inflammatory protein-1, by activating transcription factors such as activating protein-1.[11,12]

The anti-inflammatory action of curcumin has been studied in various animal model studies. Curcumin had anti-inflammatory action similar to cortisone in reducing carrageenan-induced paw oedema in mice and rats. Curcumin has been reported to reduce inflammation and improve symptoms in mice with experimentally induced colitis. The intra-peritoneal injection of curcumin extract has been shown to significantly inhibit joint inflammation in animal models.[13]

Several clinical studies have shown curcumin to have beneficial anti-inflammatory properties. Curcumin in doses of 1200 mg/day in patients with rheumatoid arthritis has been shown to benefit patients in terms of decreasing joint swelling and morning stiffness.[14] In a comparative study of 45 patients,

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post-surgical spermatic cord oedema was significantly reduced by 84.2 per cent in patients using curcumin; its effect was found to be similar to that of phenylbutazone.[13] In a cross-over, randomised, controlled trial of osteoarthritis patients, curcumin demonstrated a significant improvement in pain severity and disability scores.[15]

In clinical trials on patients suffering from lichen planus, high doses of curcumin used as oral rinses were effective in reducing the severity of mucositis.[16] An *in vitro* oral mucositis model using human pharyngeal cell line Detroit 562 exposed to bacterial stimuli and treated with curcumin, demonstrated a reduction in bacterial adherence and a decrease of pro-inflammatory cytokine release in the cell lines. Bacterial adherence and cytokine adhesion are the key initial steps in the pathogenesis of mucositis. This inhibitory action may have therapeutic benefit in the treatment of oral mucositis.[17] Animal studies have also shown curcumin to reduce radiation-induced mucositis. Topical application of curcumin reduced the severity of mucositis in rats exposed to local radiation to the tongue.[12]

Curcumin mouth rinses have been shown to benefit patients with radiation-induced mucositis. A single-blinded, randomised, comparative clinical study was conducted on head and neck SCC patients treated by radiation or chemoradiation. Curcumin mouth rinses were compared with povidone-iodine mouthwashes in 80 patients. The curcumin group had delayed-onset and less severe mucositis compared to the povidone-iodine groups, which was statistically significant ($p < 0.001$). Fourteen out of 39 patients developed high-grade mucositis in the curcumin group, whereas 34 of 40 patients in the povidone-iodine group developed high-grade mucositis.[17]

Research papers have described the poor pharmacokinetic and pharmacodynamic properties of curcumin.[18,19] The relative oral bioavailability of the combination of curcuminoid and essential oil of turmeric with turmerones (BCM-95) is 6.93-fold higher than that of normal curcumin.[20] The presence of turmerones inhibits p-glycoprotein, thereby increasing the permeability of curcumin.[21]

The synergic effect of curcumin and turmerones and its anti-inflammatory potential were reported in a paper in which inflammation-associated mouse colon carcinogenesis was prevented and in an animal model of dextran sodium sulphate induced colitis.[22,23] The dietary supplementation of curcuminoids with essential oil of turmeric in obese cats expressed a beneficial effect on inflammatory markers.[24] A previous study on the topical application of bioavailable curcumin in rats supported its wound healing effect.[25] *In vitro* and *in vivo* studies of bioavailable curcumin and metformin have stated that this is an efficient combination for chemoprevention, based on the clinical response and associated inhibition of cancer stem cells.[26] The combination of curcuminoid and essential oil of turmeric was found to confer a radioprotective effect in patients with prostate cancer by reducing the severity of radiotherapy-related urinary symptoms.[27] In another study, it increased the plasma total antioxidant capacity and decreased the activity of superoxide dismutase in patients with prostate cancer who were receiving radiotherapy, without compromising the therapeutic efficacy of radiotherapy.[28]

In our study, there was no statistical difference between the groups in terms of oral mucositis severity until the end of the second week of treatment. However, from the third week, mucositis severity in group A (turmeric extract (study) group) was significantly lower compared to that in group B (placebo (control) group). After three weeks of treatment, 86.7 per cent of patients in group A had only grade 1 mucositis, in comparison to 71 per cent with grade 2 mucositis in group B; this difference was statistically significant ($p < 0.001$). At the end of four weeks of treatment, the majority of patients (73.3 per cent) in group A had only grade 1 mucositis, while 67.7 per cent of patients in group B had grade 2 mucositis and 12.9 per cent had grade 3 mucositis. The difference was found to be statistically significant ($p < 0.001$). At follow up, two months after the completion of treatment, 86.6 per cent of patients in group A had only mild mucositis, while 77.5 per cent of patients in group B had grade 2 mucositis and 3.2 per cent ($n = 1$) had grade 3 mucositis.

Mucositis is a complex process. At the cellular level, radiation damages DNA, generates free radicals, releases cytokines and activates NFκB. Various *in vitro* and *in vivo* studies have shown that curcumin inhibits the activity of NFκB, thereby decreasing the release of inflammatory cytokines and leading to scavenging free radicals.[12] This could reflect the protective action of curcumin in reducing the oral mucositis.

The lack of systemic toxicity and the diverse inhibitory effect of turmeric extract on various inflammation pathways makes it an ideal agent in the treatment of radiation-induced mucositis. As highlighted in our study, turmeric extract can significantly reduce mucositis severity, which can benefit patients undergoing radiation or chemoradiation.

- Bioavailable turmeric extract (500 mg) thrice daily (1.5 g/day) reduced the incidence and severity of radiation-induced mucositis
- Combination of curcuminoid and essential oil of turmeric with turmerones increased the bioavailability of curcumin in turmeric extract
- At the cellular level, radiation causes: DNA damage, free radical generation, cytokine release and nuclear factor kappa B (NFκB) activation
- Turmeric extract inhibits NFκB activity, thereby decreasing: inflammatory cytokine release, scavenging free radicals and bacterial adherence
- No systemic toxicity was observed; turmeric extract is safe to use
- Turmeric extract is ideal for head and neck cancer patients undergoing radiotherapy or concurrent chemoradiation

Conclusion

Oral administration of bioavailable turmeric extract (1.5 g/day) reduced mucositis severity when compared to patients in a control group who underwent the same modality of treatment but without the turmeric extract. Turmeric extract can reduce the severity of mucositis, benefitting patients undergoing radiation or chemoradiation. No systemic toxicity was associated with the intake of turmeric extract in our study.

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Competing interests. None declared

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