Open Labelled Pilot Study of Topically Applied Curcumin Versus Standard Treatment on Chronic Wound Healing

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ABSTRACT

Introduction: Failure of the timely and orderly reparative process to establish the anatomic and functional integrity results in chronic wound. Inflammation is essential for normal wound healing, but an unchecked inflammation hampers the healing process. Any agent that effectively reduce excess inflammation can be useful in wound healing. The objectives of this study were to evaluate the efficacy of topical curcumin in healing of the chronic wounds and also to study its effect on NF- kB and COX-II expression levels in chronic wound tissues compared to controls receiving standard treatment.

Material and Methods: This is a pilot study conducted in 20 patients with chronic ulcer, divided into two equal groups. A comparision was done between two groups who were treated with topically applied curcumin ointment versus our standard treatment protocol for wound management. All these patients were evaluated clinically, qunatitative bacterial culture and expression of molecular markers in the wound.

Results: The efficacy of curcumin on wound contraction rate, accrural of granulation tissue, epithelizartion and reduction in bacterial colony count was not statistically significant compared to standard treatment protocol. Expression levels of proinflammatory genes mainly COX-2, TNF-α, IL-6, IL-1b was reduced and NF-κB translocation into the nucleus was also inhibited in curcumin treated group compared to standard treatment protocol.

Conclusion: Although there was no difference in both the groups in its clinical parameters, curcumin treated group showed underexpression of pro-inflammatory genes and inhibition of translocation of NF-κB which have a barrier role on the excess inflammation. This favours the positive role of curcumin on treating the chronic wounds.

Keywords: Curcumin, Wounds, Ulcer, Inflammation, Turmeric, Wound Healing.

INTRODUCTION

The management of chronic wounds of various aetiologies entails a substantial burden in terms of money and manpower at treating institutions, apart from the reduction in the physical and mental health related quality of life.[1] The management of these ulcers hinges on effective wound care, use of systemic medications to mitigate secondary infections and psychological support during the period of convalescence. Currently, role of phytochemicals in healing of wound is under investigation.[2] *Curcuma longa* commonly called as turmeric, one of the popular spice in India that has been used in treating various ailments due to its anti-inflammatory effects.[3] The main curcuminoid in turmeric is curcumin (diferuloylmethane) which produces the yellow color. The anti-inflammatory, anti-microbial, anti-oxidant, and wound healing effects of curcumin have been shown in studies.[4,5] It hastens the healing by acting on various natural stages of the healing process of wound. The objectives of our study was to evaluate the efficacy of topical curcumin in the healing of chronic wounds and to study its effect on the expression levels of NF- kB and COX-II in chronic wound tissues on comparision to the control group receiving standard care.

MATERIAL AND METHODS

Patients attending our out-patient department for chronic wound management from November 2015 to December 2016 were included in this study after obtaining the informed and written consent. Patients with ulcers of any etiology, present on any part of the body for 3 weeks or more, and meeting other requisite inclusion criteria mentioned below were eligible for recruitment. Other inclusion criteria were: 1) age > 18 years; 2) hemoglobin level > 10gms % and total WBC not more than 11,000/mm^3; 3) wound swab culture showing at least one of the following organisms- Pseudomonas aeruginosa, Streptococcus pyogenes or Escherichia coli; and 4) willingness and ability to fully participate for the entire duration of the study. All patients with immunosuppressive conditions, active complicated cardiovascular diseases, uncontrolled diabetes, and blood urea and serum creatinine > 15% of upper limit of normal laboratory range were excluded from the study. Also, patients with osteomyelitis, septic arthritis, necrotizing fasciitis, gas gangrene and

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infected prosthetic device or foreign body were not included. Appropriate antibiotics were given systemically if cellulitis or invasive infection was present clinically.

Patients were allocated into two groups. Group A consisted of patients with ulcers treated by topically application of curcumin ointment was used, whereas Group B consisted of patients for whom only standard treatment protocol was used. Standard treatment protocol included daily cleaning using betadine saline solution and dressing with oxum soaked gauzes. An ayurvedic physician was also a part of this study to oversee the usage of curcumin.

Measurement of the wound was done as the product of the greatest diameters in two dimensions. Digital photographs with a ruler placed alongside the wound were obtained initially and then again after 2 and 4 weeks of treatment. 0.5 x 0.5 cm biopsy was taken from the wound bed, taking care to exclude necrotic tissue. Swab culture and sensitivity was taken to obtain data about the infecting pathogen/s. Cultures were obtained at 2 weeks and on completion of the study at 4 weeks. The ulcers were categorized according to their size as upto 20sq cms, 21-50sq cms, 51-90sq cms and more than 90sq cms.

Assessment of wound healing

The clinical parameters used to assess the degree of wound healing were,

- Percentage of wound contraction was categorized as i) no contraction, ii) >10% to 25% contraction, and iii) more than 25% contraction.
- Percentage of area of the ulcer covered by epithelium (epithelialization) was categorized as i) less than 50%, ii) between 50% to 99%, and iii) 100%.
- Percentage of wound covered by granulation tissue was scored as, 1+ (Less than 25% of wound area), 2+ (25 to 50% of wound area), and 3+ (>50% of wound area).

Microbiological evaluation

Assessment of bacterial load was performed using the Quantitative Swab Technique. The number of organisms in the wound was reported as log10 of the colony forming units (cfu/cm^2). Both aerobic and anaerobic load was studied. The isolates of Pseudomonas aeruginosa, Streptococcus pyogenes and Escherichia coli were subjected to further study. When required, the mini API identification system (BioMerieux) was used for identification.

Immunohistochemical analysis for determination of NF-kB:

Tissue taken were fixed in 10% buffered formalin, paraffin embedded and sectioned into 5 micron thick slices on silanated slides. Antigen retrieval and further staining was done as per standard protocols using commercially available target retrieval solution (Dako, USA), antibody to NF-κB phospho p65 (ser 536), secondary antibody from the Vectastain Elite kit and stained with DAB (3, 3' Diaminobenzidine) with hematoxylin as counter stain. The levels of NF-κB were measured by immunohistochemistry for phospho NF-kB localization. A semi quantitative technique where the intensity of the stain, progressively characterized as 1, 2 or 3, was multiplied by the number of cells showing positive staining to obtain a histoscore. Mean histoscore of tissues obtained pre and post curcumin treatment was determined statistically.

Biopsy from the wound bed was taken before starting the treatment and then again after 4 weeks for characterizing mRNA profile of genes associated with modulation of inflammatory pathways.

Total RNA extraction was done after multiple step centrifugation in RNeasy spin column.

RNA quantity and quality were determined using Nanodrop (ND-1000 spectrophotometer).

STATISTICAL ANALYSIS

Fischer's exact test was applied to test the statistical significance of mean values of wound size reduction, reduction in bacterial load, percentage area of ulcer covered by granulation tissue, percentage of epithelialization, COX II, TNF-a, IL-1b, IL-6 expression between the two groups. Mcnammars' test was used to test the statistical significance within the group. P value < 0.05 is considered statistically significant.

RESULTS

Twenty patients were included in the study and divided into two groups, each having 10 patients. The age range was between 20-70 years. Except for one patient in group B who had ulcer over left distal forearm**,** remaining all patients had ulcers in the lower limb. Figure 1 shows the type of ulcers in both the groups. All the patients had a single ulcer.

Quantitative culture

Multiple organisms were isolated from each ulcer. Among the isolates, those with a significant colony count were selected as the primary organisms. The main organism isolated in all the ulcers was Pseudomonas aeruginosa. (Table 1)

On comparision of quantitative bacterial culture between

Organisms Isolated	Group A (Curcumin) n = 10			Group B (Non curcumin) n = 10		
	Day 0	2 weeks	4 weeks	Day 0	2 weeks	4 weeks
Pseudomonas aeruginosa	9	8	9	7	4	5
Escherichia coli	2	1	1	4	1	2
Proteus mirabilis	1	2	-	1	1	-
Proteus vulgaris	1	-	2	-	2	-
Staphylococcus aureus	-	-	-	-	1	3

Table-1: Organisms isolated from each ulcer

No. of cfu/ml at 4 weeks	Group A (Curcumin group) n (%)	Group B (Non-curcumin group) n (%)	p value
> 1x10^5	1 (10%)	0	1.0
< 1x10^5	9 (90%)	10 (100%)	

Table-2: Quantitative bacterial culture at the end of 4 weeks.

No. of cfu/ml	Group A at Day 0 n (%)	Group A at 4 weeks n (%)	p value
> 1x10^5	1 (10%)	1 (10%)	1.0
< 1x10^5	9 (90%)	9 (90%)	

Table-3: Comparison within group A pre and post treatment (curcumin group).

No. of cfu/ml	Group B at Day 0 n (%)	Group B at 4 weeks n (%)	p value
> 1x105	1 (10%)	0	1.0
< 1x105	9 (90%)	10 (100%)	

Table-4: Comparison within group B pre and post treatment (Non-curcumin group).

Size of Ulcer: Pre-treatment	Group A (Curcumin) n (%)	Group B (Non-curcumin) n (%)
Upto 20 sq cms	0	5 (50)
21-50 sq cms	6 (60)	3 (30)
51-90 sq cms	3 (30)	2 (20)
>90 sq cms	1 (10)	0

Table-5: Size of Ulcer at Day 0 (Pre-treatment).

Percentage of wound contraction	Group A (Curcumin) n (%)	Group B (Non-curcumin) n (%)
No contraction	4 (40%)	5 (50%)
>10 to 25%	4 (40%)	3 (30%)
> 25%	2 (20%)	2 (20%)

Table-6: Wound contraction at 4 weeks (Post treatment).

Percentage of wound contraction	Group A (Curcumin) n (%)	Group B (Non curcumin) n (%)	p value
≤ 25%	8 (80%)	8 (80%)	1.0
> 25%	2 (20%)	2 (20%)	

Table-7: Percentage of ulcer contraction at the end of 4 weeks post treatment.

the groups at the end of 4 weeks showed no statistically significant difference. (Table 2)

Within the groups pre treatment (Day 0) and post treatment (4 weeks) as well, there is no difference in the quantitative bacterial culture. (Table 3 and 4)

Wound Contraction:

The ulcers in both the groups according to its size is shown in table 5. Maximum wound contraction was observed at 4 weeks in both the groups (Figure 2 and 3). The percentage

Area covered by granulation tissue	Group A (Curcumin) n (%)	Group B (Non curcumin) n (%)	p value
≤ 50%	2 (20%)	5 (50%)	0.350
> 50%	8 (80%)	5 (50%)	

Table-8: Percentage of ulcer granulation at the end of 4 weeks post treatment.

Percentage of wound epithelialization	Group A (Curcumin) n (%)	Group B (Non curcumin) n (%)	p value
≤ 50%	2 (20%)	2 (20%)	1.0
> 50%	8 (80%)	8 (80%)	

Table-9: Percentage of ulcer epitheliallization at the end of 4 weeks post treatment.

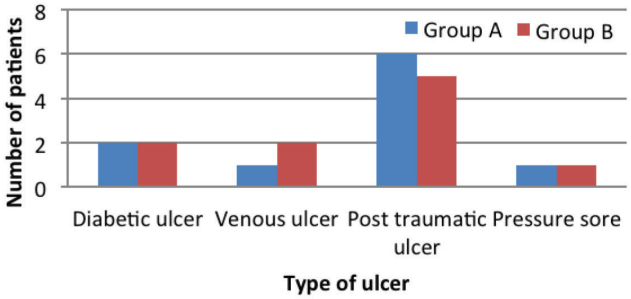

Figure-1: Distribution of ulcers in both groups according to etiology.

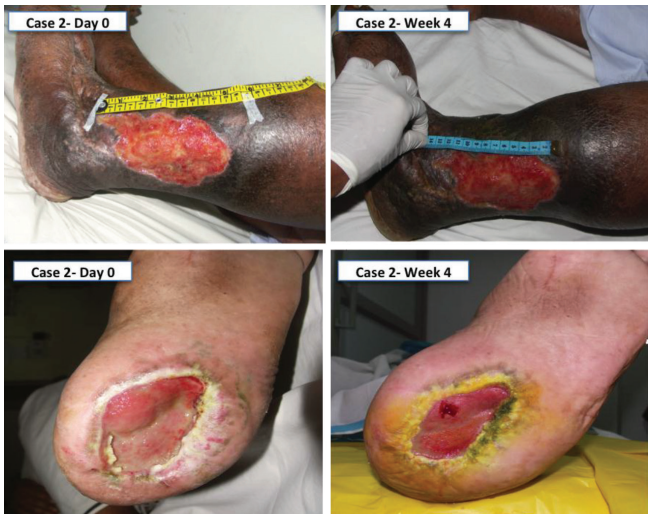

Figure-2: Photographic representation of wound at 0 and 4 weeks in curcumin group showing wound contraction and granulation.

of wound contraction is shown in table 6. The mean wound contraction for group A was 20.23% as compared to 14.4% in group B (Figure 4).

Wound contraction at the end of 4 weeks showed slightly better in group A when compared to group B, but it was not statistically significant.(Table 7)

Appearance of granulation tissue

Although number of ulcers showing >50% area of accrural of granulation tissue were eight in Group A as compared to five in group B, there was no statistical significance. (Table 8)

Gene	Group A (Curcumin)		Group B (Non curcumin)		p value
	Under expression	No change/ Over expression	Under expression	No change/ Over expression	
COX2	60%	40%	30%	70%	0.37
IL-1b	60%	40%	60%	40%	1.0
IL-6	70%	30%	30%	70%	0.17
TNFα	80%	20%	40%	60%	0.17

Table-10: Gene expressions at the end of 4 weeks post treatment.

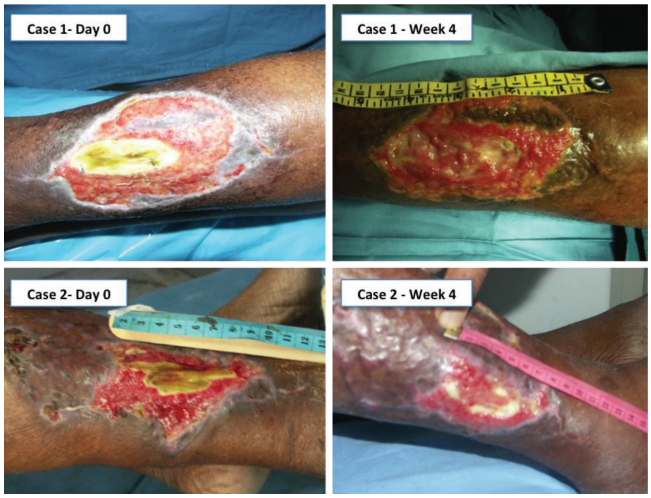

Figure-3: Photographic representation of wound at 0 and 4 weeks in non-curcumin group showing wound contraction and granulation.

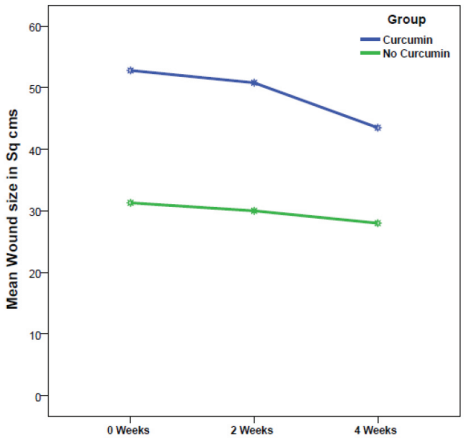

Figure-4: Graphic representation of wound contraction periodically.

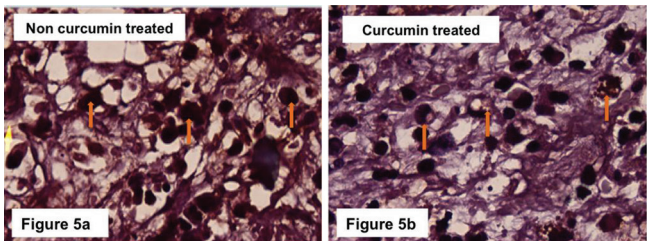

Figure-5a and b: Immunohistochemistry: Antiphospho p-65 antibody against p-65 in NF-kB followed by DAB staining. 5a shows DAB staining is seen in both nucleus and cytoplasm as dark brown in non-curcumin group. 5b shows DAB sDDAB staining toplasm as dark brown and nucleus stained with hematoxylin stain.

Epithelialization of the wound

Wound epithelialization showed no difference between the groups at the end of 4 weeks. (Table 9)

Immunohistochemistry for NF-kB and RT-PCR for COX-2:

NF-kB was localized in both the groups from the tissue slides taken on day 0 (Pre treatment). In group A, after 4 weeks of treatment, only four showed a faint staining of NF-kB in the nucleus (Figure 5b). Remaining showed no staining. In group B, at 4 weeks, there was a significant increase in the expression of NF-kB in the nucleus and thus dark staining in eight (Figure 5a). The other two showed faint staining in the nucleus.

Determination of COX-2 gene expression by RT-PCR method

The COX-2 gene amplification by RT-PCR and its hybridization with COX-2 oligonucleotide probe showed an increase in the transcript abundance of COX-2 in tissue samples from group B (n=7) after 4 weeks of standard treatment protocol. There was abundance of the transcript from the samples at day 0 in the same group. In group A tissue samples, although there was abundance of the expression of COX-2 gene at day 0, the number of transcripts of COX-2 mRNA at 4 weeks after treatment showed reduction in the number and six tissue samples had under expression of the gene as compared to three in group B.

The levels of TNFα had been under expressed in eight patients in group A as compared to four in the group B. Although the p value is not significant statistically, there is considerable under expression of the COX-2, TNFα, IL-6, and IL-1b gene in group A when compared to group B as shown in Table 10.

DISCUSSION

Wound healing is a complex and dynamic mechanism which changes according to individual health status of the patient. Self resolving transient inflammation is an essential prerequisite for fibroblast activation and matrix synthesis in wound healing but, a state of sustained inflammation has been shown to abrogate wound healing.[6] The sustained production of inflammatory mediators and inflammatory cells influx results in imbalance of wound proteases and their inhibitors. This prevents matrix synthesis and remodelling which is necessary for wound healing.[7,8] The host inflammatory response is regulated by induction of cytokine genes which is mediated by nuclear factor kappa B (NF-κB). This transcription factor NF-κB is produced by a number of microbial components. Activation of NF-κB results in dimerization and translocation into the nucleus where it binds to target genes and regulates their transcription. The role of NF-κB has been implicated in the production of proteases like the MMPs which have been shown to be very high in non healing wounds and reductions in the level of proteases have been demonstrated with the onset of healing.[9] Thus,

interventions to inhibit NF-kB can be potentially beneficial in the healing of chronic wounds.[6]

Curcumin is a polyphenol derived from Curcuma longa, commonly known as turmeric.[2] It belongs to ginger family and its rhizomes produce a brilliant yellow dye. The primary bioactive constituents were phenolic curcuminoids, of which curcumin (diferuloylmethane) is the most important. Curcumin reduces the secretion of cytokines in the wound and promotes the wound healing in various wound models.[10-13] It is also a good antioxidant[14-17] and radioprotective agent.[12,18] It has been shown to inhibit TNF by reducing its effect in fibroblast lytic assay.[19] The anti-inflammatory effect of curcumin is because of its free radical scavenging activity.[20,21] The main therapeutic limitation is its rapid plasma clearance and conjugation. This has led to investigate the conjugation of various substances with curcumin to increase its systemic bioavailability.[22] An extensive research till date has demonstrated the usage of topically applied curcumin only in experimental animals. In this background, this study was conducted to evaluate its benefit in chronic wound management.

The contraction of wound is a centripetal movement of edges of the wound to facilitate closure of the defect.[23] The clinical assessment of the wound contraction periodically will show the progression of wound healing. Although there has not been any published data on topically applied curcumin on the wounds in humans, an animal study done by Jagetia[10-12] et al, concluded that curcumin treatment accelerates the healing of irradiated wounds by enhancing the synthesis of collagen, hexosamine, DNA, and nitrate. Sidhu[13,14] et al, showed migration of macrophages, fibroblasts, and myofibroblasts into the wound. They also showed epidermal re-epithelialization and faster wound healing in curcumin treated animals. They also observed increase in collagen deposition, TGF-b1, and fibronectin in curcumin treated wounds. Panchatcharam[15] et al, in their study on cutaneous wound healing in rats concluded that curcumin application has decreased the lipid peroxides level, while glutathione peroxidase, superoxide dismutase, catalase levels were increased significantly and exhibit the antioxidant effect of curcumin in enhancing wound healing. In our study, wound contraction has not been significantly different on comparison between the groups. The ulcers in our study were mainly located in the lower extremity and the wound healing depends on various factors like the vascularity of the limb and venous disorders which may account for the disparity in the findings between ours and the animal studies. The essential component of wound healing is neovascularization and formation of healthy granulation tissue. The granulation tissue is a good media for migration of the epidermal cells from the wound margins. Curcumin treatment in animal studies showed increase in granulation tissue, neovascularisation and faster re-epithelialisation of the wound. Sidhu[13,14] et al showed higher vessel density with better epithelialisation rate and earlier organization of wound due to enhanced collagen deposition in curcumin treated wounds. This again in humans depends on the individual patient, site of the ulcer, etiology of the ulcer, vascularity of the limb on which the ulcer is situated. After 4 weeks of treatment with topically applied curcumin and the standard regimen, there was no significant difference in the granulation tissue fromation as well as epithelialization. But the curcumin treated wounds looked healthier clinically.

The microbiological study in the form of quantitative swab culture yielded mainly Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Proteus vulgaris, and Proteus mirabilis in both the groups. There was no significant difference in bacterial colony counts in both the groups post treatment but there has been a trend towards reduction in colony forming units of the bacteria from the wound culture after curcumin application.

Even though the clinical wound assessment showed no significant between the two groups, the molecular level changes were in favour of curcumin treated group. Medina E[24] et al and Naumann M[25] et al showed that the bacterias are involved mainly in the stimulation of secretion of NF-kB from the cells. Chiu J et al[26], have concluded that application of topical curcumin resulted in down regulation of NF-kB. Curcumin inhibits the translocation of phosphorylated NF-kB into the nucleus, resulting in down regulation of transcription of genes implicated in the initiation of inflammation. The positive part of our study was the effect of curcumin on downregulation of NF-kB induction by the microorganism.

Curcumin has shown to supress experimentally induced tumorigenesis on various animal models. There is a significant evidence that targeted inhibition of COX-2 activity or expression not only alleviates inflammation, but also prevents cancer. Curcumin treatment resulted in suppression of COX-2 protein expression, mRNA and PGE2 production induced by TPA (12-O-tetradeconoylphorbol-13-acetate) on several human gastrointestinal cell lines.[27,28] The non-steroidal anti-inflammatory drugs inhibits only the COX-2 catalytic activity. Our results showed that curcumin can inhibit expression of the COX-2. The same inference has been supported by Chun KS et al[29] in their study. Although there is evidence of overexpression of COX-2 gene in four ulcers in curcumin treated group, they had larger size ulcers and more bacterial colony forming units as compared to the ulcers in standard treatment group which also showed over expression of COX-2.

NF-kB is one of the transcription factor activated during the initiation of inflammation. This up-regulates the production of TNF which induces the production of IL-l. The pro-inflammatory cytokines TNF and IL-l affects the entire body and induce the expression of variety of genes and proteins that induce acute and chronic inflammation. TNF activates NF-kB reciprocally. TNF and IL-l also potentiate each other's production. This leads to escalation of their own levels like an autocrine loop, resulting in pathogenesis of many inflammatory diseases. This has been studied by Chan MM[19] et al in animal studies, who showed that application of curcumin to the wound resulted in reduced expression of TNF-a and IL-1b. There is underexpression of TNF-a, IL-1b

in curcumin group as compared to standard treatment group in our study. Although there is reduction of IL-6 expression in seven tissue samples from curcumin group, it does not significantly show any difference from the non-curcumin group.

This study has its own limitations. The number of patients was small to have a good statistical correlation. There is lack of data in the literature regarding the nature of curcumin ointment, its strength as well as duration of application as there was no prior human studies on application of curcumin. Hence these factors could have affected the outcome of the study and may be the reason why the biochemical improvements didn't reflect in the clinical findings.

CONCLUSION

This pilot study was done to evaluate the role of topically applied curcumin on healing of chronic wounds. Although no significant difference in clinical parameters on both the groups, biochemical reduction of chronic inflammatory mediators was seen with curcumin application as seen from the underexpression of COX-2, TNF-a, and IL-1. NF-kB translocation into the nucleus had significantly reduced in the curcumin treatment group compared to those on the standard treatment. This was not reflected in the clinical or bacteriological findings. Probable reasons could be due to inadequate strength, contact time of curcumin and the small sample size, thus not allowing a good statistical correlation. Hence a study with large patient number along with increase in the dose and contact time of curcumin ointment application might yield more optimal results.

List of abbrevations

NF-kB – Nuclear Factor-kappa b, COX-2 – Cyclo-oxygenase 2 gene, TNF-a – Tumour necrosis factor alpha, IL-1b – Interleukin 1 beta, IL-6 – Interleukin 6, IL-8 – Interleukin 8, MMP – Matrix metalloproteinases, MAP – Mitogen activated protein, Gy – Gray, TGF-b – Tissue growth factor beta, CFU – colony forming unit, ml – milliliters, ROS - Reactive oxygen species

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