# *Original Article*

# A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications

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## Abstract

**Background:** Chronic cutaneous complications such as pruritus are among the very frequent complaints of sulphur mustard (SM)-exposed patients. The present trial investigated the impact of curcumin on serum inflammatory biomarkers and their association with pruritus severity and quality of life (QoL).

**Methods:** This was a randomized, double-blind trial among 96 male Iranian veterans (age 37–59 y) who were suffering from chronic SM-induced pruritic skin lesions. Patients were randomly assigned to curcumin (1 g/d, $n = 46$) or placebo ($n = 50$) for four weeks. Serum concentrations of interleukins 6 (IL-6) and 8 (IL-8) together with high-sensitivity C-reactive protein (hs-CRP) and calcitonin gene-related peptide (CGRP) were measured at baseline and at the end of the trial. Assessment of pruritus severity was performed using the pruritus score and QoL using the Dermatology Life Quality Index (DLQI).

**Results:** Serum IL-8 and hs-CRP were significantly reduced in both groups but the magnitude of reduction was greater in the curcumin group ($P < 0.001$). Serum CGRP was only decreased in the curcumin group ($P < 0.001$). No significant change was observed in serum IL-6. There were significant correlations between CGRP and IL-6 changes ($P = 0.011$) and between DLQI and IL-8 changes ($P = 0.026$) in the curcumin group. In the curcumin group, changes in serum IL-8 concentrations were found as the significant predictor of DLQI scores ($P = 0.026$) but none of the independent variables could predict pruritus scores.

**Conclusions:** Curcumin supplementation effectively mitigates inflammation in patients suffering from chronic SM-induced cutaneous complications. This anti-inflammatory effect might account for the observed pruritus alleviation and QoL improvement by this phytochemical.

## Introduction

Sulphur mustard ($C_4H_8Cl_2S$; 2,2-dichlorethyl sulphide; SM), is a toxic chemical warfare agent with potent alkylating and blistering properties. Since its discovery, SM has been extensively used in military conflicts. The last military deployment of SM dates back to the Iraq–Iran war (1983–1988), in which the Iraqi army repeatedly used this agent against Iranian soldiers and civilians.[1] It is estimated that over 100,000 Iranians have been exposed and chemically injured with SM, of whom about one-third currently suffer from chronic complications.[2] Although the pathophysiology of SM toxicity has not been fully clarified, DNA damage and resulting inflammatory and oxidative responses are considered as cornerstones of pathological effects.[3,4] Along with lungs and eyes, skin is among the most sensitive organs to SM that could undergo several types of damage based on the SM dose and duration of exposure.[3,5] Cutaneous complications of SM have been chronologically classified into acute and chronic. Chronic complications of SM are present even 20 y after exposure, and have been frequently reported in Iranian intoxicated patients. These complications include pruritus, xerosis, pigmentation disorders, pain, erythema, scarring and burning sensation.[6–8] Among these symptoms, pruritus has been reported to be the most common complaint, being present in about 70–90% of intoxicated patients.[9] In a recent study, Panahi *et al.*[10] found a significant negative impact of pruritus on the quality of life (QoL) of chemically injured patients who suffer from chronic SM-induced complications. However, current available medications for SM-induced pruritus are limited and mostly based on symptomatic therapy with topical corticosteroids. On the

other hand, long-term application of topical corticosteroids is associated with significant adverse effects including steroid atrophy, rosaceae, striae, telangiectasis and increased bruisability.[11]

One promising candidate to combat chronic complications of SM is the dietary polyphenol, curcumin. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione; diferuloyl methane] is the yellow pigment and major bioactive constituent in the dried rhizomes of *Curcuma longa* L. (turmeric). There is ample evidence indicating a wide variety of biological and pharmacological activities for curcumin including anti-inflammatory, antioxidant, cardio- and neuroprotective, chemopreventive, anti-cancer and many more effects.[12,13] One key advantage of curcumin is its safety and tolerability. It has been shown that oral doses of curcumin up to 12 g/d are well tolerated in humans.[14]

Owing to the pivotal contribution of inflammation and oxidative stress to the pathogenesis of SM-induced cutaneous complications, safe medications with dual anti-inflammatory and antioxidant activity would be highly desirable for the management of symptoms. In a recent trial, we reported remarkable improvement of pruritus, QoL and antioxidant status following supplementation with curcumin.[15] However, it remains unclear whether mitigation of systemic inflammation by curcumin has a role in the positive observed effects. Hence, the present study investigated the impact of curcumin on serum inflammatory biomarkers and their association with pruritus severity and QoL.

## Methods

### Participants

This study was a randomized, double-blind and placebo-controlled clinical trial, performed in the Veterans Clinic of Tehran and Ilam (west of Iran).[16] Included subjects were male Iranian veterans of the Iraq–Iran war (age range: 37–59 y) who were suffering from chronic pruritic skin lesions. The exposure was confirmed by documented development of blisters in the exposed areas of the skin and transient visual deterioration lasting for several days and associated respiratory symptoms. Patients were excluded if itching resulted from systemic or cutaneous non-chemical diseases, or if they had received any topical treatments within one month prior to the study.

Included patients ($n = 96$) were randomized to receive curcumin (1 g/d) (curcumin group; $n = 46$) or matched placebo (placebo group; $n = 50$) for a period of four weeks. The groups were matched regarding age ($47.5 \pm 10.7$ and $48.3 \pm 8.5$ in the curcumin and placebo group, respectively). Curcumin was administered in the form of C3 Complex® capsules (Sami Labs LTD, Bangalore, Karnataka, India) containing 500 mg curcuminoids plus 5 mg bioperine®. Bioperine® is an extract obtained from black pepper (*Piper nigrum* L.) or long pepper (*Piper longum* L.), and contains 95% piperine which is a well-documented bioavailability enhancer. Placebo capsules used in the study were shape- and size-matched, and contained piperine (5 mg).

**Table 1** Calculation details of pruritus score

| | Morning | Afternoon | Night | Overall |
|---|---|---|---|---|
| **Period** | 1 | 1 | 1 | 3 |
| **Severity** | | | | |
| Itching without the need to scratch | 1 | 1 | – | 10 |
| Itching with an occasional need to scratch | 2 | 2 | – | |
| Frequent scratching | 3 | 3 | – | |
| No itching relief with scratching | 4 | 4 | – | |
| Itching with discomfort all the time | 5 | 5 | – | |
| **Distribution** | | | | |
| Arms | 1 | 1 | – | 10 |
| Trunk | 1 | 1 | – | |
| Legs | 1 | 1 | – | |
| Head | 1 | 1 | – | |
| Face | 1 | 1 | – | |
| Generalized itching | 5 | 5 | – | |
| **Frequency** | | | | |
| Itching in 2 periods of less than 10 min or 1 period of more than 10 min | 1 | 1 | – | 10 |
| Itching in 10 periods of less than 10 min or 5 periods of more than 10 min | 5 | 5 | – | |
| **Sleep duration** | | | | |
| Seven hours or more of night sleep (0 points) | | – | 0 | 10 |
| Absence of sleep (10 points) | – | – | 10 | |
| **Waking up** | | | | |
| For each awakening due to pruritus (1 point); maximum of 5 points for 5 or more episodes | – | – | | 5 |
| **Overall** | 16 | 16 | 16 | 48* |

*Maximum obtainable score

Patients were visited by a board-certified dermatologist at baseline and at the end of treatment duration. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Baqiyatallah University of Medical Sciences and written informed consent was obtained from participants.

### Assessment of pruritus severity

Assessment of pruritus severity was performed using pruritus score. This is a questionnaire-based score in which the entire 24-h period has been divided into three periods: morning (the time from getting up until noon), afternoon (the time from noon until going to bed) and night. A single point was allocated for report of pruritus in each period, to a maximum of three points for a patient who complained of pruritus during all three periods. The scores of severity, distribution and frequency of pruritus were recorded separately for the morning and the afternoon as shown in Table 1.

## Assessment of QoL

QoL was evaluated using the Dermatology Life Quality Index (DLQI). DLQI has been previously employed in Iranian patients with SM-induced chronic skin lesions.[10] This index consists of 10 questions under six headings: symptoms and feelings (questions 1 and 2), daily activities (questions 3 and 4), leisure (questions 5 and 6), work and school (question 7), personal relationships (questions 8 and 9) and treatment (question 10). Each question has a maximum score of 3 and options of 'very much' (scored 3), 'a lot' (scored 2), 'a little' (scored 1) and 'not at all' (scored 0). In addition, a '0' score is allotted to 'not relevant' response and unanswered questions. DLQI total score is calculated by summing the scores of all questions, resulting in a scoring range of 0–30 in which higher scores are associated with more severe impairments of QoL.

## Biochemical analyses

Blood samples were collected at baseline and at the end of the trial. Collected samples were centrifuged at $750\,g$ for 10 min to obtain serum. Serum samples were then kept at $-80°C$ prior to analysis. Serum concentrations of interleukins 6 (IL-6) (Assay Designs Inc., Farmingdale, NY, USA) and 8 (IL-8) (Assay Designs Inc.) together with calcitonin gene-related peptide (CGRP) (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA) were measured using commercial enzyme immunoassay kits. Serum high-sensitivity C-reactive protein (hs-CRP) was determined using an immunoturbidimetric assay (Pars Azmoon Co., Tehran, Iran).

## Statistical analyses

Statistical analyses were performed using SPSS software for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). Data were expressed as mean $\pm$ SD. Data were assessed for normality using the Kolmogorov–Smirnov test. Group comparisons were made using independent samples $t$-test and paired samples $t$-test for normally distributed data, or Mann-Whitney $U$ test and Wilcoxon signed-rank test for non-normally distributed data. Categorical variables were compared using chi-square or Fisher's exact test. Bivariate correlations between different parameters were assessed using Pearson's (for normally distributed data) or Spearman's (for non-normally distributed data) rank correlation coefficients in the curcumin and placebo groups. Stepwise multiple linear regression analysis was used to identify the independent parameters that were related to the evaluated efficacy measures. A two-tailed $P$ value of $<0.05$ was considered to be statistically significant.

## Results

Ninety-six patients entered the study, of whom 80 patients completed the study ($n = 40$ in each group) and were included in the final analyses. Six patients discontinued study treatment in the curcumin group (three because of gastrointestinal side-effects, one because of fear of side-effects, one because of inability to return to the clinic

because of the long distance and one due to unknown reason), and ten in the placebo group (seven because of lack of treatment response or worsening of symptoms, two because of gastrointestinal side-effects and one because of inability to return to the clinic because of the long distance) (Figure 1). There was no significant difference in the dropout rate between the groups ($P > 0.05$; chi-square test).

## Effect of curcumin supplementation on serum IL-6

Baseline values for serum IL-6 were comparable between the curcumin and placebo groups ($P > 0.05$; independent samples $t$-test). Serum IL-6 concentrations were found to remain statistically unchanged by the end of the trial in both the curcumin and placebo groups ($P > 0.05$; paired samples $t$-test). In the same manner, the magnitude of changes in serum IL-6 was not different between the groups ($P > 0.05$; independent samples $t$-test) (Tables 2 and 3).

## Effect of curcumin supplementation on serum IL-8

Baseline serum IL-8 concentrations were significantly higher in the curcumin compared with the placebo group ($P = 0.001$; Mann-Whitney $U$ test). Serum IL-8 concentrations were significantly decreased in both the curcumin ($P < 0.001$; Wilcoxon signed-rank test) and placebo ($P < 0.001$; paired samples $t$-test) groups. However, the magnitude of serum IL-8 reduction was remarkably greater in the curcumin group ($P < 0.001$; independent samples $t$-test) (Tables 2 and 3).

## Effect of curcumin supplementation on serum CGRP

Baseline serum CGRP levels were comparable between the curcumin and placebo groups ($P > 0.05$; independent samples $t$-test). Curcumin supplementation caused a marked decrease in serum CGRP ($P < 0.001$; paired samples $t$-test) while there was no significant difference in the placebo group ($P > 0.05$; paired samples $t$-test). With respect to the magnitude of changes, the extent of reduction was greater in the curcumin versus placebo group ($P < 0.001$; independent samples $t$-test) (Tables 2 and 3).

## Effect of curcumin supplementation on serum hs-CRP

There was no significant difference in baseline serum hs-CRP concentrations between the groups ($P > 0.05$; independent samples $t$-test). Serum hs-CRP was reduced by the end of the trial in both the curcumin and placebo groups ($P < 0.001$; paired samples $t$-test). Nevertheless, the magnitude of reduction was significantly greater in the curcumin group ($P < 0.001$; independent samples $t$-test) (Tables 2 and 3).

## Effect of curcumin supplementation on pruritus score

Pruritus scores were comparable between the curcumin and placebo groups at baseline ($P > 0.05$; independent samples $t$-test). Supplementation with curcumin was associated with a marked decline in pruritus score ($P < 0.001$; paired
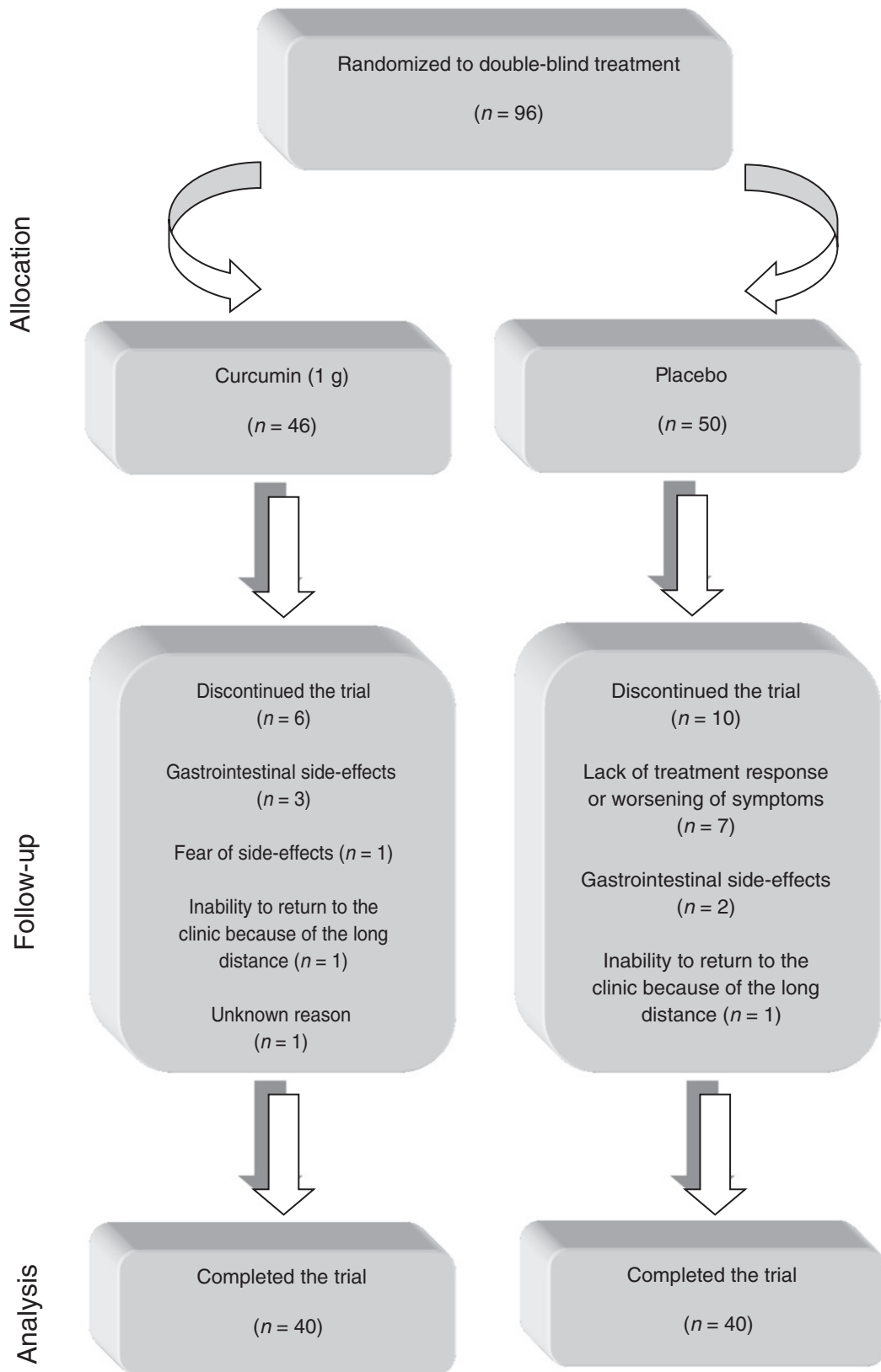
**Figure 1** Flowchart of the trial

**Table 2**   Within-group comparison of the evaluated biochemical parameters and efficacy measures

| | Curcumin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Pretrial | Post-trial | P value | Pretrial | Post-trial | P value |
| IL-6 | $0.73 \pm 0.21$ | $0.77 \pm 0.36$ | 0.563 | $0.67 \pm 0.12$ | $0.67 \pm 0.15$ | 0.773 |
| IL-8 | $34.67 \pm 4.47$ | $24.28 \pm 2.71$ | $<0.001$ | $31.04 \pm 4.83$ | $27.09 \pm 3.47$ | $<0.001$ |
| CGRP | $45.79 \pm 4.60$ | $39.88 \pm 3.92$ | $<0.001$ | $43.89 \pm 4.69$ | $43.59 \pm 4.52$ | 0.531 |
| Hs-CRP | $2.58 \pm 0.59$ | $1.46 \pm 0.42$ | $<0.001$ | $2.53 \pm 0.49$ | $2.29 \pm 0.46$ | 0.001 |
| PS | $40.60 \pm 3.43$ | $28.23 \pm 4.95$ | $<0.001$ | $40.10 \pm 4.31$ | $39.48 \pm 3.40$ | 0.23 |
| DLQI | $35.63 \pm 3.85$ | $24.78 \pm 5.22$ | $<0.001$ | $34.23 \pm 4.12$ | $32.13 \pm 4.65$ | 0.003 |

Values are expressed as mean $\pm$ SD

IL, interleukin; CGRP, calcitonin gene-related peptide; Hs-CRP, high-sensitivity C-reactive protein; PS, pruritus score; DLQI, Dermatology Life Quality Index

**Table 3**   Between-group comparison of the evaluated biochemical parameters and efficacy measures

| | Curcumin | Placebo | P value |
|---|---|---|---|
| IL-6 | $0.04 \pm 0.44$ | $0.005 \pm 0.11$ | $>0.05$ |
| IL-8 | $-10.40 \pm 5.05$ | $-3.96 \pm 4.52$ | $<0.001$ |
| CGRP | $-5.90 \pm 4.06$ | $-0.30 \pm 3.06$ | $<0.001$ |
| Hs-CRP | $-1.13 \pm 0.50$ | $-0.24 \pm 0.44$ | $<0.001$ |
| PS | $-12.37 \pm 5.24$ | $-0.62 \pm 3.24$ | $<0.001$ |
| DLQI | $-10.85 \pm 6.28$ | $-2.10 \pm 4.23$ | $<0.001$ |

Values are expressed as mean $\pm$ SD

IL, interleukin; CGRP, calcitonin gene-related peptide; Hs-CRP, high-sensitivity C-reactive protein; PS, pruritus score; DLQI, Dermatology Life Quality Index

samples $t$-test). In contrast, no significant difference was observed in the placebo group ($P > 0.05$; paired samples $t$-test). In the same manner, change in pruritus score was significantly greater in the curcumin versus placebo group ($P < 0.001$; independent samples $t$-test) (Tables 2 and 3).

### Effect of curcumin supplementation on QoL

Comparison of baseline DLQI scores did not indicate any significant difference between the groups ($P > 0.05$; Mann-Whitney $U$ test). DLQI was significantly decreased by the end of the trial in both the curcumin ($P < 0.001$; Wilcoxon signed-rank test) and placebo ($P = 0.003$; paired samples $t$-test) groups. However, the rate of reduction was greater in the curcumin versus placebo group ($P < 0.001$; independent samples $t$-test) (Tables 2 and 3).

### Bivariate analysis

At baseline, there were significant correlations between serum IL-6 concentrations and CGRP (Pearson's $r = 0.418$; $P = 0.007$) as well as pruritus score (Pearson's $r = -0.328$; $P = 0.039$), and between DLQI and pruritus score (Spearman's $r = 0.316$; $P = 0.047$) in the curcumin group while no significant correlation was found in the placebo group. As for the post-trial values, serum IL-6 concentrations were significantly correlated with serum CGRP (Pearson's $r = 0.400$; $P = 0.011$) in the curcumin group. There was also a significant inverse correlation between pruritus and DLQI scores (Pearson's $r = -0.404$; $P = 0.010$) in the curcumin group. The only significant correlation that was observed in the placebo group was between serum IL-8 and pruritus score (Pearson's $r = -0.363$; $P = 0.021$). Bivariate associations were also

checked for the changes in the evaluated biochemical and efficacy measures. Only two significant correlations were found in the curcumin group: between CGRP and IL-6 changes (Pearson's $r = 0.397$; $P = 0.011$) and between DLQI and IL-8 changes (Pearson's $r = 0.351$; $P = 0.026$). Correlation graphs are illustrated in Figure 2.

### Multiple regression analysis

Stepwise multiple regression analysis was used to assess the impact of predictor variables on each of the employed efficacy measures. Changes (pretrial versus post-trial) in pruritus score and DLQI score were separately entered into the model as dependent variable. Predictor variables included changes in serum IL-6, IL-8, CGRP and hs-CRP concentrations. In the curcumin group, changes in serum IL-8 concentrations were found as the significant predictor of DLQI scores ($B = 0.437$; odds ratio [95% CI] $= 0.351$ [0.054–0.819]; $P = 0.026$) but none of the independent variables could predict pruritus scores. No significant determinant was found in the placebo group, neither for DLQI nor pruritus scores.

## Discussion

The purpose of the current study was to determine the impact of curcumin supplementation on circulating inflammatory markers of patients suffering from chronic SM-induced pruritic skin lesions. We also assessed the association between these alterations and observed changes in the patients' pruritus severity and QoL. A growing body of evidence has confirmed the pivotal role of inflammation in the ethiopathogenesis of both acute and chronic SM toxicity.[3,4] SM has been shown to up-regulate the expression of several proinflammatory mediators in keratinocytes, including IL-6, IL-8, tumor necrosis factor-$\alpha$ and CGRP. Such an inflammatogenic effect of SM is, at least in part, due to the activation of proinflammatory factors such as nuclear factor (NF)-$\kappa$B, mitogen-activated protein kinases and activator protein-1.[3] In addition to the inductive effect on expression, SM also increases the extracellular release of cytokines.[16] The released proinflammatory cytokines possess considerable vasoactive and chemoattractant potential, thereby promoting inflammatory cell recruitment and activation.[17] A number of findings on the induction of inflammatory biomarkers following SM exposure have been summarized in Table 4.
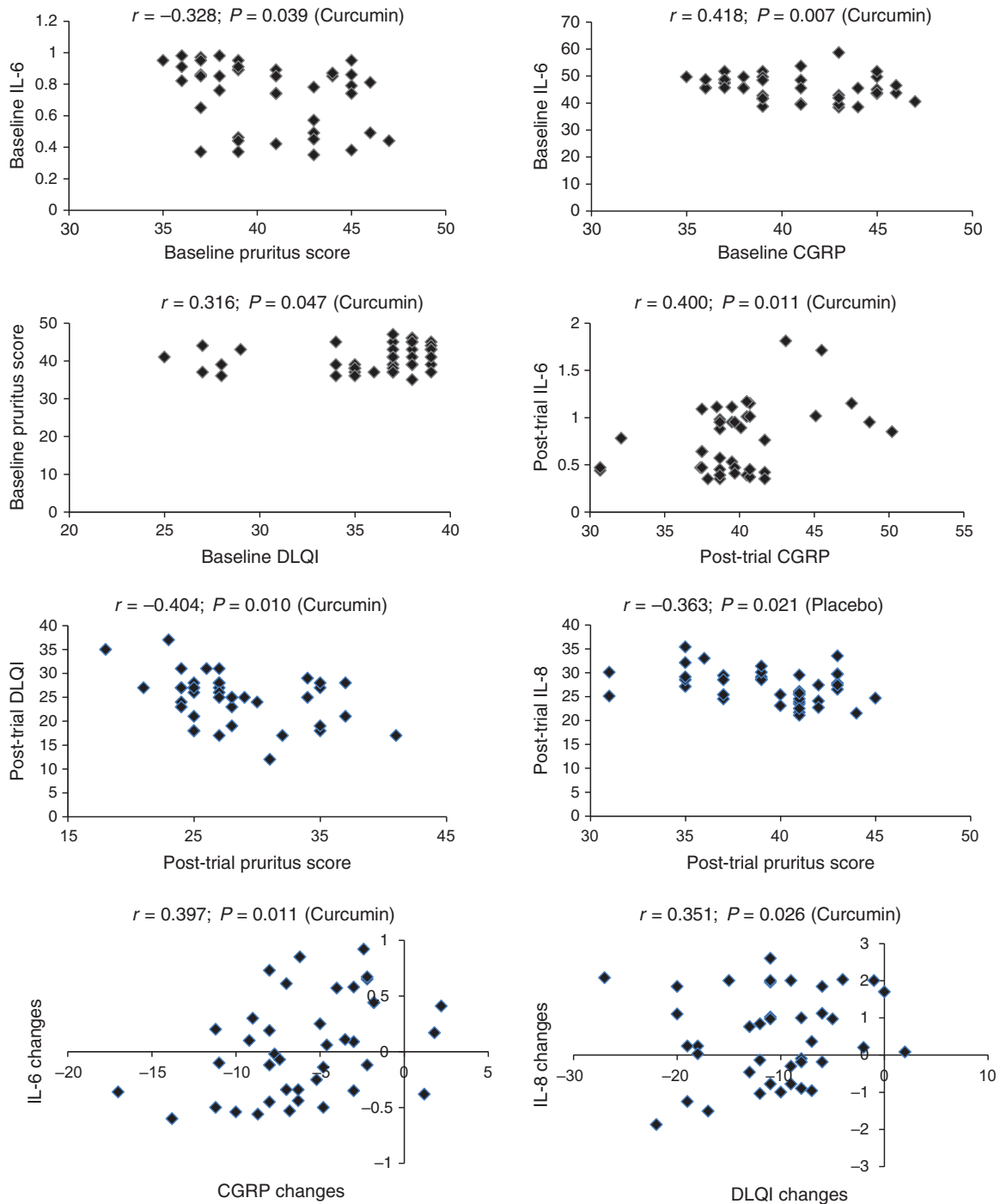
**Figure 2** Significant correlations between the evaluated efficacy measures. CGRP, calcitonin gene-related peptide; DLQI, Dermatology Life Quality Index

In the current research, a remarkable reduction of serum IL-8 was observed from curcumin that was significantly higher than that in the placebo group. This is consistent with previous findings on the effects of curcumin in other inflammatory disease states.[12,18] An important mechanism for the down-regulating effects of curcumin on proinflammatory cytokines is suppression of NF-κB by this phytonutrient.[19,20]

Further to cytokines, elevated circulating levels of hs-CRP have been reported in patients with chronic SM complications,[21] which is indicative of a heightened burden of systemic inflammation in these patients. Hs-CRP has been documented as one of the most sensitive surrogate markers of systemic inflammation in a number of diseases, including those concerning dermatology such as psoriasis vulgaris,[22] urticaria,[23] Behçet's disease,[24] papillomatosis[25] and uraemic pruritus.[26] There is both human and animal evidence indicating CRP-lowering activity of curcumin. In a clinical trial in osteoarthritis patients, administration of a phospholipidated formulation of curcumin (equivalent to 200 mg curcumin/d) for three months was associated with a

**Table 4**   A summary of previous reports on the up-regulation of inflammatory biomarkers by sulphur mustard

| Ref. | Experimental model | Findings |
|---|---|---|
| 39 | Rabbit skin | Increased expression of IL-8, MCP-1 and IL-1$\beta$ |
| 40–42 | Mouse skin | Increased expression of MMCP-1, MIP-1, MIP-2, IL-1$\beta$, IL-6, TNF-$\alpha$ and GM-CSF |
| 40,43 | Hairless mice dorsal skin | Increased expression of IL-1$\alpha$, IL-1$\beta$, MIP-1$\alpha$, MIP-2, MCP-1 and TNF-$\alpha$ |
| 44 | Weanling pigs | Increased expression of IL-1$\beta$, IL-6, IL-8 and TNF-$\alpha$ |
| 45 | Cultured human keratinocytes | Increased release of IL-1$\beta$, IL-6, IL-8 and TNF-$\alpha$ |
| 46 | Cultured skin fibroblasts | Increased expression of IL-6 |
| 47 | Cultured human neutrophils | Increased release of TNF-$\alpha$, IL-6 and IL-8 |
| 48 | Differentiated human lung cells | Increased IL-8 release |
| 49 | Hairless guinea pig skin | Increased expression of TNF-$\alpha$, IFN-$\gamma$ and IL-8 |

MIP, macrophage inflammatory protein; MMCP, mouse mast cell protease; TNF, tumour necrosis factor; MCP, monocyte chemotactic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon

significant reduction of plasma CRP concentrations.[27] Likewise, curcumin supplementation has been reported to exert the same effect on hs-CRP in low-density lipoprotein receptor-deficient (LDLR −/−) mice fed with a high-cholesterol diet[28] as well as lead-intoxicated rats[29] and weaned piglets.[30]

Another important finding of the present study was effective reduction of serum CGRP following curcumin supplementation. CGRP has been previously shown to be involved in nociception and pruritus. CGRP is expressed by keratinocytes and its levels are increased in human chronic pain or chronic pruritus conditions such as atopic dermatitis and pruritus.[31,32] CGRP also promotes inflammation through up-regulation of IL-1 and IL-8 and endothelial-leukocyte adhesion molecule 1, chemotaxis of neutrophils and translocation of P-selectin.[33,34] Regarding the contribution of this mediator to the perception of both pain and pruritus, its reduction by curcumin could represent a plausible mechanism for the promising results observed in the present study. Thus far, no study has investigated serum CGRP status and its modulation in patients suffering from chronic complications of SM. This is also the first report on the impact of curcumin on CGRP levels.

Aside from inflammation, several other mechanisms have been suggested to be implicated in the pathogenesis of SM-induced dermatotoxicity. The most important of these mechanisms include induction of DNA damage, matrix metalloproteinases, poly (ADP-ribose) polymerase signalling, nitric oxide, calcium signalling, apoptosis and oxidative stress.[17] Interestingly, there is evidence indicating the beneficial impact of curcumin on nearly all of these biochemical abnormalities.[12] For instance, curcumin not only inhibits cyclooxygenase-2, lipoxygenase and inducible nitric oxide synthase but also induces heat shock proteins that confer cytoprotection against different stimuli.[35,36] In addition, curcumin possesses well-established antioxidant and free radical scavenging activity which enables it for effective prevention of membrane lipid peroxidation as well as oxidative DNA damage and resulting genotoxicity.[37] We have previously shown in the same patients that curcumin supplementation efficiently enhances serum levels of three important enzymatic antioxidants, namely superoxide dismutase, glutathione peroxidase and catalase.[15] In light of the present findings, the efficient anti-pruritic effects and improvement of QoL by curcumin could be attributed to both antioxidant and anti-inflammatory functions of this compound.

The current findings add to a growing body of literature on the beneficial effects of curcumin in dermatological disorders. Previously, several encouraging studies have shown the efficacy of curcumin therapy in the promotion of wound healing and protection against psoriasis, scleroderma and skin cancer.[38] However, large randomized controlled trials could provide more definitive evidence using additional biomarkers of inflammation. Besides, future investigation and experimentation is warranted to clarify whether the therapeutic effects of curcumin on SM-induced cutaneous complications are enhanced at higher doses of the phytochemical. Finally, it is strongly recommended that further research be undertaken to explore the anti-inflammatory and antioxidant effects of curcumin in the amelioration of pulmonary and ocular complications of SM-exposed patients.

## REFERENCES

1 United Nations Security Council. *Report of the mission dispatched by the Secretary General to investigate allegations of the use of chemical weapons*

*in the conflict between the Islamic Republic of Iran and Iraq. S/18852 and S/18852/Addedum 1.* New York, NY: United Nations, 1987

2 Kehe K, Szinicz L. Medical aspects of sulphur mustard poisoning. *Toxicology* 2005;**214**:198–209

3 Shakarjian MP, Heck DE, Gray JP, et al. Mechanisms mediating the vesicant actions of sulfur mustard after cutaneous exposure. *Toxicol Sci* 2009;**114**:5–19

4 Ghabili K, Agutter PS, Ghanei M, Ansarin K, Panahi Y, Shoja MM. Sulfur mustard toxicity: history, chemistry, pharmacokinetics, and pharmacodynamics. *Crit Rev Toxicol* 2011;**41**:384–403

5 Balali-Mood M, Hefazi M. The clinical toxicology of sulfur mustard. *Arch Iran Med* 2005;**8**:162–79

6 Hefazi M, Maleki M, Mahmoudi M, Tabatabaee A, Balai-Mood M. Delayed complications of sulfur mustard poisoning in the skin and the immune system of Iranian veterans 16–20 years after exposure. *Int J Dermatol* 2006;**45**:1025–31

7 Khateri S, Ghanei M, Keshavarz S, Soroush M, Haines D. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. *J Occup Environ Med* 2003;**45**:1136–43

8 Momeni AZ, Enshaeih S, Meghdadi M, Amindjavaheri M. Skin manifestations of mustard gas. A clinical study of 535 patients exposed to mustard gas. *Arch Dermatol* 1992;**128**:775–80

9 Panahi Y, Moharamzad Y, Beiraghdar F, Naghizadeh MM. Comparison of clinical efficacy of topical pimecrolimus with betamethasone in chronic skin lesions due to sulfur mustard exposure: a randomized, investigator-blind study. *Basic Clin Pharmacol Toxicol* 2009;**104**:171–5

10 Panahi Y, Davoudi SM, Sadr SB, Naghizadeh MM, Mohammadi-Mofrad M. Impact of pruritus on quality of life in sulfur mustard-exposed Iranian veterans. *Int J Dermatol* 2008;**47**:557–61

11 Henqque UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol* 2006;**54**:1–15

12 Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as 'Curecumin': from kitchen to clinic. *Biochem Pharmacol* 2008;**75**:787–809

13 Epstein J, Sanderson IR, Macdonald TT. Curcumin as a therapeutic agent: the evidence from *in vitro*, animal and human studies. *Br J Nutr* 2010;**103**:1545–57

14 Lao CD, Ruffin MT IV, Normolle D, et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med* 2006;**6**:10

15 Panahi Y, Sahebkar A, Amiri M, et al. Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 2011; doi:10.1017/S0007114511006544

16 Lardot C, Dubois V, Lison D. Sulfur mustard upregulates the expression of interleukin-8 in cultured human keratinocytes. *Toxicol Lett* 1999;**110**:29–33

17 Kehe K, Balszuweit F, Steinritz D, Thiermann H. Molecular toxicology of sulfur mustard-induced cutaneous inflammation and blistering. *Toxicology* 2009;**263**:12–9

18 Abe Y, Hashimoto S, Horie T. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacol Res* 1999;**39**:41–7

19 Surh YJ, Chun KS, Cha HH, et al. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. *Mutat Res* 2001;**480–481**:243–68

20 Jobin C, Bradham CA, Russo MP, et al. Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. *J Immunol* 1999;**163**:3474–83

21 Pourfarzam S, Ghazanfari T, Yaraee R, et al. Serum levels of IL-8 and IL-6 in the long term pulmonary complications induced by sulfur mustard: Sardasht-Iran Cohort Study. *Int Immunopharmacol* 2009;**9**:1482–8

22 Coimbra S, Oliveira H, Reis F, et al. C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. *J Eur Acad Dermatol Venereol* 2010;**24**:789–96

23 Kasperska-Zajac A. Acute-phase response in chronic urticaria. *J Eur Acad Dermatol Venereol* 2012;**26**:665–72

24 Şahin E, Karaman G, Uslu M, Karul A, Şendur N, Şavk E. Adiponectin levels, insulin resistance and their relationship with serum levels of inflammatory cytokines in patients with Behçet's disease. *J Eur Acad Dermatol Venereol* 2011; doi: 10.1111/j.1468-3083.2011.04318.x

25 Tamraz H, Raffoul M, Kurban M, Kibbi AG, Abbas O. Confluent and reticulated papillomatosis: clinical and histopathological study of 10 cases from Lebanon. *J Eur Acad Dermatol Venereol* 2011; doi: 10.1111/j.1468-3083.2011.04328.x

26 Chen HY, Chiu YL, Hsu SP, et al. Elevated C-reactive protein level in hemodialysis patients with moderate/severe uremic pruritus: a potential mediator of high overall mortality. *QJM* 2010;**103**:837–46

27 Belcaro G, Cesarone MR, Dugall M, et al. Product-evaluation registry of Meriva®, a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. *Panminerva Med* 2010;**52**:55–62

28 Roshan VD, Assali M, Moghaddam AH, Hosseinzadeh M, Myers J. Exercise training and antioxidants: effects on rat heart tissue exposed to lead acetate. *Int J Toxicol* 2011;**30**:190–6

29 Shin Sk, Ha Ty, McGregor RA, Choi Ms. Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. *Mol Nutr Food Res* 2011;**55**:1829–40

30 Ilsley SE, Miller HM, Kamel C. Effects of dietary quillaja saponin and curcumin on the performance and immune status of weaned piglets. *J Anim Sci* 2005;**83**:82–8

31 Salomon J, Baran E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008;**22**:223–8

32 WiśNicka B, Szepietowski JC, Reich A, Orda A. Histamine, substance P and calcitonin gene-related peptide plasma concentration and pruritus in patients suffering from psoriasis. *Dermatol Psychosom* 2004;**5**:73–8

33 Smith CH, Barker JNWN, Morris RW, MacDonald DM, Lee TH. Neuropeptides induce rapid expression of endothelial cell adhesion molecules and elicit granulocytic infiltration in human skin. *J Immunol* 1993;**151**:3274–82

34 Tan YR, Qin XQ, Guan CX, Zhang CQ, Xiang Y, Ren YH. Influence of regulatory peptides on the secretion of interleukins from bronchial epithelial cells of the rabbit. *Acta Physiol Sin* 2002;**54**:107–10

35 Tanwar V, Sachdeva J, Golechha M, Kumari S, Arya DS. Curcumin protects rat myocardium against isoproterenol-induced ischemic injury: attenuation of ventricular dysfunction through increased expression of hsp27 along with strengthening antioxidant defense system. *J Cardiovasc Pharmacol* 2010;**55**:377–84

36 Teiten MH, Reuter S, Schmucker S, Dicato M, Diederich M. Induction of heat shock response by curcumin in human leukemia cells. *Cancer Lett* 2009;**279**:145–54

37 Kelkel M, Jacob C, Dicato M, Diederich M. Potential of the dietary antioxidants resveratrol and curcumin in prevention and treatment of hematologic malignancies. *Molecules* 2010;**15**:7035–74

38 Thangapazham RL, Sharma A, Maheshwari RK. Beneficial role of curcumin in skin diseases. *Adv Exp Med Biol* 2007;**595**:343–57

39 Tsuruta J, Sugisaki K, Dannenberg AM Jr, Yoshimura T, Abe Y, Mounts P. The cytokines NAP-1 (IL-8), MCP-1, IL-1 beta, and GRO in rabbit inflammatory skin lesions produced by the chemical irritant sulfur mustard. *Inflammation* 1996;**20**:293–318

40 Ricketts KM, Santai CT, France JA, et al. Inflammatory cytokine response in sulfur mustard-exposed mouse skin. *J Appl Toxicol* 2000;**20**:S73–6

41 Sabourin CLK, Petrali JP, Casillas RP. Alterations in inflammatory cytokine gene expression in sulfur mustard-exposed mouse skin. *J Biochem Mol Toxicol* 2000;**14**:291–302

42 Wormser U, Brodsky B, Proscura E, Foley JF, Jones T, Nyska A. Involvement of tumor necrosis factor-alpha in sulfur mustard-induced skin lesion; effect of topical iodine. *Arch Toxicol* 2005;**79**:660–70

43 Sabourin CLK, Danne MM, Buxton K, et al. Modulation of sulfur mustard-induced inflammation and gene expression by Olvanil in the hairless mouse vesicant model. *J Toxicol Cutan Ocul Toxicol* 2003;**22**:125–36

44 Sabourin CLK, Danne MM, Buxton KL, Casillas RP, Schlager JJ. Cytokine, chemokine, and matrix metalloproteinase response after sulfur mustard injury to weanling pig skin. *J Biochem Mol Toxicol* 2002;**16**:263–72

45 Arroyo CM, Schafer RJ, Kurt EM, Broomfield CA, Carmichael AJ. Response of normal human keratinocytes to sulfur mustard: cytokine release. *J Appl Toxicol* 2000;**20**:S63–72

46 Arroyo CM, Broomfield CA, Hackley BE Jr. The role of interleukin-6 (IL-6) in human sulfur mustard (HD) toxicology. *Int J Toxicol* 2001;**20**:281–96

47 Ham HY, Hong CW, Lee SN, Kwon MS, Kim YJ, Song DK. Sulfur mustard primes human neutrophils for increased degranulation and stimulates cytokine release via TRPM2/p38 MAPK signaling. *Toxicol Appl Pharmacol* 2011;**258**:82–8

48 Seagrave J, Weber WM, Grotendorst GR. Sulfur mustard vapor effects on differentiated human lung cells. *Inhal Toxicol* 2010;**22**:896–902

49 Mishra NC, Rir-sima-ah J, March T, *et al.* Sulfur mustard induces immune sensitization in hairless guinea pigs. *Int Immunopharmacol* 2010;**10**:193–9