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ORIGINAL RESEARCH

Evaluating the efficacy of curcumin plus serratiopeptidase formulation in inflammatory acne: a quasi-experimental study

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Abstract

Background: Acne vulgaris is one of the most common dermatological illnesses affecting people worldwide. In Pakistan, approximately 9.4% of the population and between 5% and 16% of young adults are affected by acne vulgaris. Conventional therapies (topical benzoyl peroxide, retinoids, antibiotics and oral isotretinoin) are effective but limited by antibiotic resistance and side effects. Curcumin (a natural anti-inflammatory/antimicrobial from turmeric) and serratiopeptidase (a proteolytic enzyme with anti-inflammatory, anti-oedematous and antibiofilm properties) each show promise in acne treatment. This article evaluates the efficacy of a combined oral curcumin plus serratiopeptidase formulation as an adjunct to inflammatory acne therapy.

Methods: Fifty individuals with mild-to-moderate symptoms of inflammatory acne participated in this quasi-experimental study. They were allocated to standard therapy alone (topical regimen: benzoyl peroxide 5% and adapalene 0.1% gel; oral doxycycline 100 mg once daily) or standard therapy plus a daily curcumin (500 mg) + serratiopeptidase (10 mg) supplement (adjunctive therapy). Acne severity was assessed using a visual analogue scale (VAS) and lesion improvement scale at baseline, 1 week and 2 weeks of treatment. Data were analysed with parametric tests after normalization (log transformation), with significance set at $p<0.05$.

Results: Baseline characteristics were similar between groups (mean age: 23 years; 66% female). Both groups showed significant improvement in mean VAS (from 7.5 at baseline to 3.1 at 2 weeks; $p<0.001$). The adjunctive therapy group achieved a markedly higher complete/near-complete improvement rate by week 2 (84% *versus* 28%; $p<0.001$). No serious adverse events occurred.

Conclusion: Curcumin plus serratiopeptidase, as an adjunct to standard therapy significantly, accelerated the resolution of inflammatory acne lesions within 2 weeks, with excellent tolerability. This novel combination targets inflammatory pathways and could reduce reliance on prolonged antibiotics. Larger, longer-term studies are recommended to confirm these findings and evaluate effects on relapse and scarring.

Keywords: acne vulgaris, anti-inflammatory therapy, curcumin, quasi experimental, serratiopeptidase.

Citation

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Introduction

Acne vulgaris is a prevalent condition characterized by persistent inflammation of the pilosebaceous units, manifesting as comedones, papules, pustules or nodules. It is most prevalent in adolescents – up to 85% of teenagers are affected – but also persists into adulthood in a significant proportion (approximately 43–66% in adults).[1] Globally, acne ranks among the top ten diseases by prevalence (estimated 9.4% of the world population.[2] In Pakistan, community studies report an acne prevalence

of 5% in the undergraduate medical students and higher rates (14–17%) in young women.[3,4] Beyond its dermatological manifestations, acne can impose a substantial psychosocial burden, with negative effects on self-esteem, social interactions and mental health. Indeed, it has been noted that no single disease causes more psychological trauma than acne vulgaris,[5,6] underscoring the need for effective treatment.

Standard acne therapy is guided by disease severity. Mild acne is managed with topical agents such as benzoyl peroxide and retinoids, with the addition of topical antibiotics (e.g. clindamycin) for inflammatory lesions. Moderate cases often require oral antibiotics (typically tetracyclines) combined with topicals, whilst severe nodulocystic acne warrants oral isotretinoin or hormonal therapy in women.[1,7] These treatments target the core pathogenic factors – follicular hyperkeratinization, *Cutibacterium acnes* (formerly *Propionibacterium acnes*) proliferation, sebum excess and inflammation. However, limitations of current therapies include increasing microbial resistance (especially *C. acnes* resistance to macrolides and tetracyclines) and adverse effects such as skin irritation (with retinoids/benzoyl peroxide), gastrointestinal upset (antibiotics), and teratogenic or systemic effects (isotretinoin). Consequently, there is growing interest in adjunctive or alternative treatments that are safe and effective and can modulate inflammation without contributing to antibiotic resistance.[8]

Curcumin, the active polyphenol in turmeric, has well-documented anti-inflammatory, antioxidant and antimicrobial properties. It downregulates inflammatory cytokines (such as IL-1β, IL-6 and TNF) by inhibiting NF-κB and other signalling pathways, and can exert direct antibacterial effects.[9] In dermatology, curcumin and turmeric preparations have been explored for psoriasis, atopic dermatitis, wound healing and acne.[10] A 2016 systematic review noted that oral or topical curcumin/turmeric products led to significant improvement in the severity of various skin diseases in 10 out of 18 clinical studies, suggesting curcumin as a promising therapeutic agent.[11] Specific to acne, curcumin has demonstrated the ability to suppress *C. acnes*-induced inflammation: for example, blue-light-activated curcumin can inhibit *C. acnes in vitro* and reduce inflammatory lesions.[12] Curcumin is also reported to reduce sebaceous gland activity and lipid peroxidation involved in acne pathogenesis.[13] These multifactorial actions make it an attractive adjunct in acne management, especially to mitigate inflammation and bacterial overgrowth.

Serratiopeptidase (serrapeptase) is a proteolytic enzyme derived from *Serratia* bacteria, used in systemic enzyme therapy for its anti-inflammatory and fibrinolytic effects. It has been used for decades in Europe and Asia to treat conditions such as arthritis, sinusitis, post-operative swelling and trauma.[14,15] Serratiopeptidase hydrolyses inflammatory exudates and dead tissue, thereby reducing oedema and facilitating tissue repair. Additionally, it is a powerful anti-inflammatory agent with analgesic and anti-oedematous properties, and even a degree of antimicrobial activity, particularly against biofilm-forming bacteria.[14,16] Notably, *in vitro* studies show that serratiopeptidase can disrupt bacterial biofilms and enhance antibiotic penetration. Clinically, combining this enzyme with antibiotics has been found to improve outcomes in infectious and inflammatory processes.[17] In acne vulgaris, early evidence hinted that serratiopeptidase as an adjuvant could accelerate lesion resolution when added to conventional therapy.[18] By cleaving inflammatory mediators and downregulating pro-inflammatory cytokines (via inhibition of COX1/COX2, 5-LOX and other pathways), serratiopeptidase may rapidly alleviate the redness and pain of inflamed acne lesions. Furthermore, its fibrinolytic action might reduce the likelihood of fibrosis and scarring.[15,19]

Curcumin and serratiopeptidase each target inflammatory pathways in acne through complementary mechanisms. We hypothesized that a combination of these two agents would have a synergistic effect in reducing inflammatory acne lesions more quickly and effectively than standard treatment alone. To date, no published clinical trial has evaluated the combined use of curcumin and serratiopeptidase in acne. A recent trial using a different enzyme (bromelain) plus curcumin showed significant reductions in acne-associated inflammation and erythema,[20] supporting the concept of enzyme-enhanced anti-inflammatory therapy. We designed this study to fill the research gap and provide evidence on the efficacy and safety of an oral curcumin plus serratiopeptidase formulation as adjunctive therapy in patients with inflammatory acne. The objective was to determine whether adding this combination to standard acne treatment improves clinical outcomes (lesion count and severity) and speeds up recovery compared with standard treatment alone.

Materials and methods

This study employed a non-randomized, quasi-experimental, pre-post design, conducted in tertiary care hospitals in Pakistan between January and June 2024. Participants were assigned based on availability and timing, without randomization. After receiving approval from the institutional ethical review board (reference No. ERC/2024/DERM/129(A)), the research procedure was implemented, and written informed consent was obtained from all participants. We enrolled patients with mild-to-moderate inflammatory acne vulgaris, defined as acne with papules

and pustules (with or without comedones), and no more than a few small nodules, corresponding to grade 2–3 acne severity. Group A received standard acne treatment (described below) plus the curcumin/serratiopeptidase supplement, and Group B received standard treatment alone.

Calculations were made to determine the size of the sample based on an anticipated modest effect size in acne severity reduction with adjunct therapy. Using Cochran's formula for comparing proportions, we calculated the sample size with the following assumptions: a confidence level of 95%, power of 80%, baseline improvement rate of 50% and expected post-intervention rate of 75% (i.e. a 25% absolute effect size). This yielded a requirement of 22 participants per group. To account for possible attrition and to enhance statistical robustness, we enrolled 25 participants per group (total n=50).[20]

Inclusion criteria were age 15–35 years, clinical diagnosis of mild or moderate inflammatory acne (with inflammatory lesion count 10–50), and no acne treatment in the past 4 weeks. Both male and female patients were eligible; female patients of childbearing age had to be non-pregnant (confirmed by test) and using contraception due to the unknown systemic effects of the supplement in pregnancy. Exclusion criteria included severe nodulocystic acne requiring isotretinoin, exclusively comedonal acne (non-inflammatory), any systemic inflammatory disease or immunosuppressive medication use, known allergy to turmeric/curcumin or serratiopeptidase, and use of other herbal or oral acne remedies in the past month. Patients with significant acne scarring or hyperpigmentation were not excluded but those findings were documented separately as they were not the focus of the outcome assessment.

All participants received standard therapy appropriate for their acne severity as per guidelines.[1,7] This consisted of a topical regimen (benzoyl peroxide 5% wash once daily, and adapalene 0.1% gel at night) for all patients. Additionally, a moderate systemic therapy was given to both groups: oral doxycycline 100 mg once daily, as it is a first-line antibiotic for moderate inflammatory acne. Group A (intervention) received an oral supplement capsule containing curcumin (500 mg) plus serratiopeptidase (10 mg), once daily after a meal. Group B (control) received an identical-appearing placebo capsule (filled with inert cellulose) once daily. The supplements (active and placebo) were manufactured and quality-tested to ensure similar appearance and taste. Both groups continued treatment for 4 weeks, which was considered an adequate period to observe initial clinical response and any accelerated improvement due to the supplement. All other aspects of management were kept constant between groups. Patients were provided with a gentle cleanser and non-comedogenic moisturizer and advised on general skincare. No intralesional steroid injections or additional procedures were performed during the study.

The primary outcome was the change in acne severity over 2 weeks, assessed by two methods: (1) inflammatory lesion counts (number of papules/pustules) on the face, recorded at baseline, week 1 and week 4 for a quantitative secondary outcome. (2) An Investigator's Global Assessment of improvement, categorized as 'Improved' (meaning clear/almost clear or >75% lesion reduction), 'Partially improved' (some improvement <75% reduction) or 'No change/worse'. This simple clinical improvement scale was adapted from prior acne trials and was applied at each follow-up by a dermatologist blinded to group allocation. In addition, a visual analogue scale (VAS) for overall acne severity (patient rated on a 0–10 scale, where 0 = clear skin and 10 = worst-ever severity) was used. This captures the patient's subjective assessment of their acne's severity, pain and/or inflammation. The percentage of patients who achieved a decrease in the number of inflammatory lesions by >50% and patient-reported satisfaction at week 2 (yes/no) were secondary outcomes. Safety outcomes included any reported adverse events (with special attention to gastrointestinal discomfort, as serratiopeptidase can cause mild gastrointestinal upset, and to rash or allergy, as curcumin can seldom cause contact dermatitis).

Participants were evaluated at baseline (Day 0), 1 week (Day 7) and 4 weeks (Day 30). At baseline, demographic data (age, sex) and acne history were noted. A visual grading of acne severity was conducted, and baseline VAS was recorded. At each follow-up, the VAS and investigator improvement scale were recorded, and lesion counts were performed. Lesion counts were manually recorded by the same dermatologist at all-time points to ensure consistency. Although digital photographs were captured at each visit to support documentation, lesion evaluation was based on direct clinical examination. Blinding of the assessor was not implemented due to logistical limitations. Adherence to medications was assessed by capsule count and patient diary. Participants were queried about any side effects or new symptoms at each visit. Compliance with topical and oral standard treatments was also reinforced and recorded.

Statistical analyses

All analyses were performed using IBM SPSS Statistics version 25. Continuous variables, such as VAS scores and inflammatory lesion counts, were reported as mean ± standard deviation (SD). Categorical variables (e.g. clinical improvement status) were summarized as frequencies and percentages. The normality of

continuous data distributions was assessed using the Shapiro–Wilk test. Although VAS scores showed mild skewness at follow-up ($p<0.05$), the distributions were sufficiently symmetrical for group comparisons using parametric methods. Independent samples *t*-tests were used to compare group differences in VAS scores and lesion counts at each time point (baseline, week 1 and week 4). Between-group comparisons of categorical outcomes, including the proportion of patients achieving 'Improved' status or >50% lesion reduction, were performed using the χ^2 test. Effect sizes were presented as mean differences or risk differences, along with corresponding 95% confidence intervals (CIs) to enhance interpretability. A *p* value of <0.05 was considered statistically significant.

Results

A total of 60 patients were assessed for eligibility; ten were excluded (six did not meet inclusion criteria and four declined participation). Fifty patients were enrolled (Group A: $n=25$; Group B: $n=25$). All completed the 4-week follow-up. Table 1 summarizes the baseline characteristics. The mean age was 23.0±3.9 years, with an age range of 15–32 years. The sample was 66% female (33/50) and 34% male. The two groups were similar in age distribution and sex ratio ($p=0.77$ and $p=0.45$, respectively). At baseline, 63.3% of participants had moderate acne and 38.7% mild acne by clinical assessment. The mean baseline inflammatory lesion count was 22.5±8.4, with no significant difference between Group A and Group B (mean 23.7 *versus* 20.9; $p=0.28$). Mean baseline VAS severity scores were also comparable: 7.6±1.3 in the supplement group *versus* 7.4±1.1 in controls ($p=0.54$). All patients had facial acne; 12% also had mild truncal acne.

Both groups showed improvement in acne severity over the 4-week treatment period, but improvements were more pronounced in Group A. Figure 1 illustrates the trajectory of mean VAS scores. At week 1, Group A had a mean VAS of 5.6±1.2 *versus* 5.1±1.1 for Group B (lower is better). Both were improved from baseline but between-group differences in VAS at 1 week were not statistically significant ($p=0.15$), indicating that, by day 7, both groups had similar moderate improvements. At 4 weeks, the mean VAS score was 3.1±1.6 in Group A *versus* 3.1±1.2 in Group B, with a between-group difference of 0.01 (95% CI −0.73 to 0.75; $p=0.94$), indicating no significant difference in VAS scores.

Despite this, a striking difference emerged in the distribution of clinical improvement between groups, as assessed by the investigator's global improvement scale. By week 4, a significantly higher proportion of patients in Group A achieved 'Improved' status (84% *versus* 28%), corresponding to a risk difference of 56% (95% CI 33.3–78.7%; $p<0.001$) (Table 2).

A faster and greater reduction in inflammatory lesion count was observed in Group A compared to standard treatment alone (Figure 2). At baseline, both groups had comparable lesion counts, but by week 1, Group A showed a more pronounced reduction (12.4 *versus* 14.2 lesions). By week 4, Group A had a mean lesion count of 8.1 *versus* 12.3 in Group B, with a mean difference of −4.2 lesions (95% CI −8.2 to −0.2; $p=0.04$), favouring the curcumin plus serratiopeptidase group. More patients in group A achieved >50% lesion reduction by week 4 (93% *versus* 71%; $p=0.03$), with a risk difference of 22% (95% CI 2.3–41.6%). Notably, 10 (40%) patients in Group A had zero papules/pustules by day 14 (full clearance), compared to 2 (8%) patients in Group B ($p=0.02$).

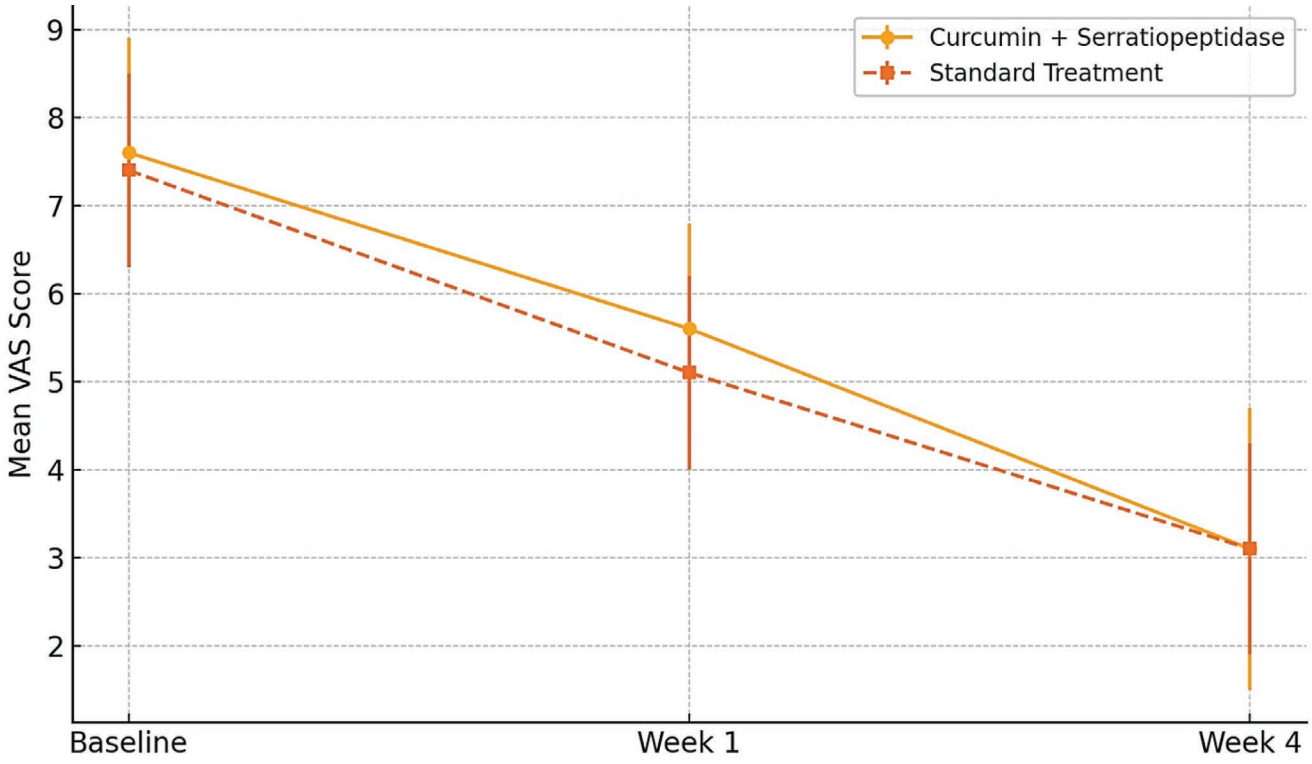
Both treatments were well tolerated. In Group A, 1 (3.4%) patient reported mild epigastric discomfort in the first few days of taking the supplement, which resolved spontaneously and did not require stopping medica-

Table 1. Baseline characteristics of patients (mean ± SD or *n* [%]).

Characteristic	Curcumin + serratiopeptidase (A) (*n*=25)	Standard treatment (B) (*n*=25)	*p* value (Group diff)
Age (years)	23.3±3.8	22.8±4.1	0.77
Female (percent)	20 (69.0%)	13 (61.9%)	0.58
Mild *versus* moderate acne	11 mild, 18 moderate	8 mild, 13 moderate	0.75
Inflammatory lesion count	23.7±8.9	20.9±7.5	0.28
VAS severity score (0–10)	7.59±1.27	7.38±1.12	0.54
Prior treatment (% patients)	4 (13.8%)	2 (9.5%)	0.69

No statistically significant differences at baseline; *p* values by *t*-test or χ^2.

Figure 1. Mean acne severity over time at baseline, week 1 and week 4.



Time point	Group A (mean ± SD)	Group B (mean ± SD)	*p* value (between groups)
Baseline	7.6±1.3	7.4±1.1	0.54
Week 1	5.6±1.2	5.1±1.1	0.15
Week 4	3.1±1.6	3.1±1.2	0.94

Table 2. Clinical improvement status at week 4.

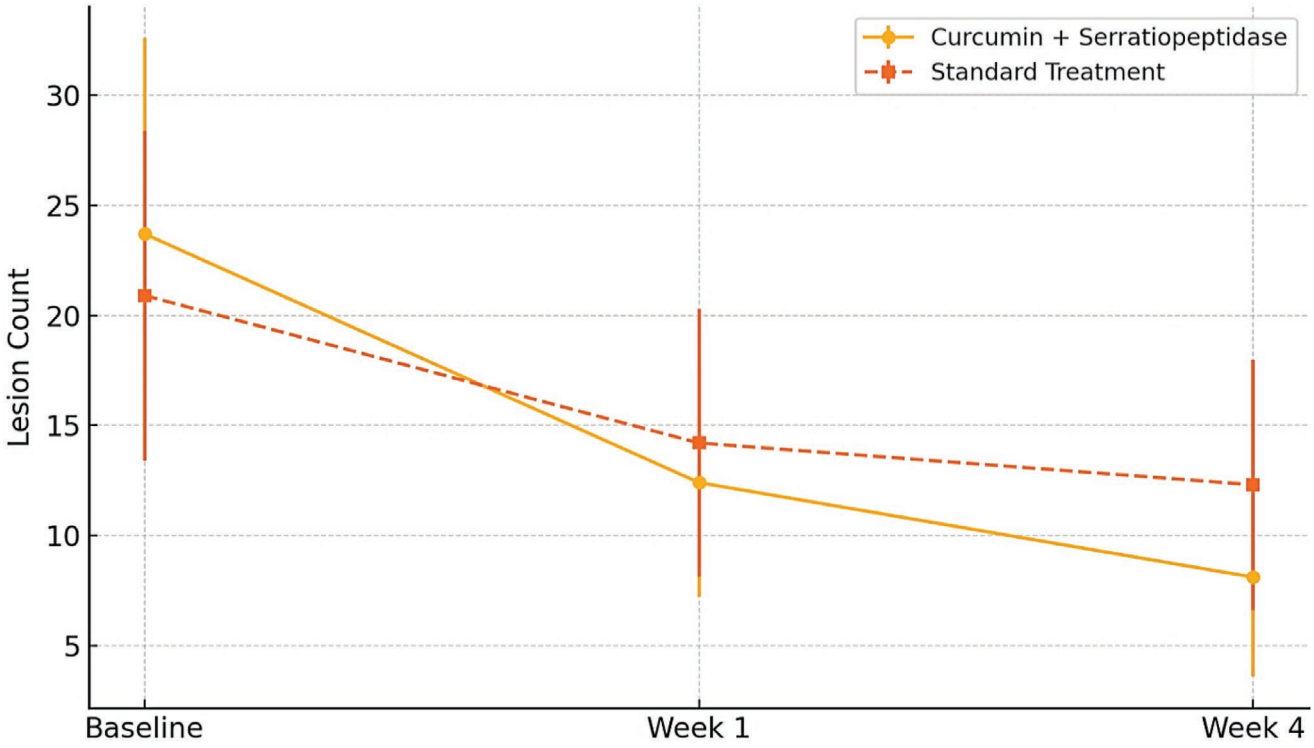
Group	Improved *n* (%)	Partially improved *n* (%)	Total (*n*)	*p* value
Group A	21 (84)	4 (16)	25	<0.001
Group B	7 (28)	18 (72)	25	

tion. No other significant adverse events were noted in the adjunctive therapy group. In Group B, no adverse events were reported. There were no cases of allergic reactions or abnormal lab results in either group. Specifically, liver function tests at 2 weeks showed no elevation from baseline in the adjunctive therapy group, consistent with the known safety of curcumin at dietary doses. Adherence to the oral supplement was 97% as per pill counts (a total of 5 missed doses among 29 patients), and adherence to doxycycline and topicals was similarly high and not different between groups. Thus, the addition of curcumin plus serratiopeptidase did not compromise compliance or safety. The overall patient-reported satisfaction at 2 weeks was higher in Group A (90% 'satisfied' *versus* 60% in control; p=0.01), reflecting the better clinical outcomes.

Discussion

This study investigated a novel combination of curcumin and serratiopeptidase as an adjunctive therapy for inflammatory acne and found that it significantly

Figure 2. Reduction in inflammatory lesion count over time at baseline, week 1 and week 4.



Time point	Group A (mean ± SD)	Group B (mean ± SD)	*p* value (between groups)
Baseline	23.7±8.9	20.9±7.5	0.28
Week 1	12.4±5.2	14.2±6.1	0.10
Week 4	8.1±4.5	12.3±5.7	0.04

enhanced treatment efficacy, especially in achieving faster and more complete lesion clearance. To our knowledge, this is the first experimental study to evaluate this specific combination in acne vulgaris. The results align with and build upon findings from prior studies that individually examined anti-inflammatory supplements for acne. For instance, Mikhael et al. reported that adding serratiopeptidase to routine acne treatment led to quicker improvement in lesion healing.[18] Our trial corroborates the beneficial role of serratiopeptidase, now in combination with curcumin, demonstrating a clear adjuvant effect by the 2-week mark. Similarly, the potent anti-acne potential of curcumin observed in earlier research is reflected in our outcomes. A recent split-face trial from China using curcumin-mediated photodynamic therapy (curcumin applied topically and activated by blue light) showed a ~59% reduction in inflammatory lesion counts, significantly superior to light therapy alone.[21] We observed an analogous magnitude of inflammatory lesion reduction (80% *versus* 66% with standard care), achieved with systemic curcumin in a non-light-dependent manner. This suggests that the anti-inflammatory and antimicrobial actions of curcumin can translate into meaningful clinical improvement even without photodynamic augmentation.

The results of our study are likewise in agreement with those obtained by Shojaan et al.,[20] who administered an oral supplement containing bromelain and curcumin to individuals with scarring from acne. They found that the enzyme plus curcumin group had significantly reduced erythema and inflammation compared to placebo. Bromelain, like serratiopeptidase, is a proteolytic enzyme with anti-inflammatory effects, and curcumin was postulated to provide synergistic benefits.[20] The success of bromelain-curcumin in reducing inflammatory sequelae of acne supports the concept that combining proteolytic enzymes with anti-inflammatory phytochemicals can yield enhanced outcomes. Our study extends this concept to active inflammatory acne lesions and demonstrates clinical efficacy in an

acne population. Notably, the time frame of 4 weeks for significant results in our trial is relatively short for acne therapies, which typically require 6–12 weeks for maximal effect. The adjunctive curcumin plus serratiopeptidase appears to accelerate the initial resolution of acne lesions. This is clinically important because faster control of inflammation can prevent long-term sequelae; early reduction of active lesions is known to lower the risk of post-inflammatory hyperpigmentation and scarring.[22] Indeed, early intervention is a primary goal in acne management to mitigate scarring. By achieving a high clearance rate in just 4 weeks, the curcumin-serratiopeptidase formulation could serve as a valuable booster in acute management of flares or moderate acne cases, possibly shortening the required duration of antibiotic use.

Pakistani patients often have skin of colour (Fitzpatrick type III–V) and are prone to post-inflammatory hyperpigmentation; a faster calming of inflammation (as seen with our supplement) could be particularly beneficial in this context to reduce pigmentary sequelae. Although we did not specifically measure hyperpigmentation outcomes, future studies could evaluate whether adjunct curcumin (which can also reduce melanogenesis) might lessen post-inflammatory hyperpigmentation in acne.

Another point of discussion is antibiotic stewardship: given the rising antibiotic resistance, especially in *C. acnes*,[8] non-antibiotic alternatives are highly sought. Curcumin has direct antimicrobial effects that might reduce reliance on antibiotics, and serratiopeptidase has been noted to enhance antibiotic activity, allowing potentially lower doses.[14] In a broader sense, nutraceutical and herbal supplements for acne are gaining popularity. A meta-analysis of herbal medicine trials in acne found significant efficacy of certain botanical topical treatments.[23] Moreover, a 12-week trial of an oral nutraceutical containing antioxidants and anti-inflammatory ingredients showed reductions in acne lesions comparable to antibiotics.[24,25]

In our adjunctive therapy group, inflammatory lesion counts were reduced by approximately 80% within just 4 weeks, which is a notably fast and robust response. Standard treatments, such as oral doxycycline combined with topicals, typically show 50–70% lesion reduction over a period of 8–12 weeks, depending on baseline severity and adherence.[26] A recent clinical trial using doxycycline with trifarotene reported similar levels of reduction albeit over a longer treatment duration of 8 weeks or more. In contrast, the adjunctive use of curcumin plus serratiopeptidase in our study achieved rapid and marked improvement in just 4 weeks, with 34% of patients showing complete clearance by day 14.[27] This suggests that the combination may accelerate the early resolution of acne inflammation.

Our study also found that curcumin plus serratiopeptidase did not compromise compliance or safety. Although no clinical signs of interaction were observed, curcumin and serratiopeptidase are known to influence drug metabolism pathways (e.g. CYP450, P-glycoprotein). Their co-administration with doxycycline may warrant further pharmacokinetic evaluation in future trials to ensure safety.

Conclusion

In conclusion, this study provides evidence that an oral curcumin plus serratiopeptidase formulation can significantly enhance the treatment of inflammatory acne when used as an adjunct to standard therapy. The combination was associated with faster reduction of inflammatory lesions and a higher rate of near-complete clearance at 4 weeks, without added side effects. These findings support the hypothesis of a synergistic effect between curcumin and serratiopeptidase, leveraging their anti-inflammatory and anti-bacterial properties to target acne pathophysiology. For patients and clinicians, such an adjunct offers a promising option to achieve better and quicker acne control, which is particularly valuable in preventing acne complications and improving patient confidence.

Limitations of the study

This study has several limitations. The modest sample size and short 4-week follow-up limit conclusions regarding long-term efficacy or relapse. Additionally, potentially relevant variables, such as Fitzpatrick skin type, hormonal influences and dietary factors, were not captured. All patients received standard acne therapy (doxycycline and topicals), which may confound the attribution of effects solely to the adjunctive supplement. Additionally, the study was non-randomized and unblinded; lesion counts were performed by a single assessor without allocation concealment, introducing potential observer bias. Although digital photographs were taken for documentation, automated lesion analysis was not used. Pharmacokinetic interactions between curcumin, serratiopeptidase and doxycycline were not evaluated. Nevertheless, these preliminary findings suggest that curcumin plus serratiopeptidase may offer meaningful adjunctive benefits. Future larger-scale, randomized trials with longer follow-up and comprehensive baseline profiling — ideally with a three-arm design — are warranted to isolate efficacy and validate these outcomes.

Contributions: SJ, KNK and FZ designed the study; MAK and NM designed the statistical plan analysis and performed all analyses. MM and SB designed the database, collected data, and clinically followed-up the patients. MAK and NM interpreted data and drafted the manuscript. SJ, KNK, FZ, MM and SB reviewed the manuscript for important intellectual contents. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: Helix Pharma provided the curcumin + serratiopeptidase supplement used in this study. NM has a professional affiliation with Helix Pharma. The company had no role in study design, data analysis, interpretation, or manuscript preparation. All assessments and analyses were conducted independently. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/06/dic.2025-4-2-COI.pdf

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