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The Effect of Oral Bromelain on Interleukin-6 Levels in Tissue of Acne Vulgaris Model Rats

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ABSTRACT

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit associated with *Cutibacterium acnes* colonization and activation of the Toll-like receptor–NF-κB pathway, which upregulates production of inflammatory mediators such as interleukin-6 (IL-6). Bromelain, a proteolytic enzyme derived from pineapple (*Ananas comosus*), is known to possess anti-inflammatory properties; however, experimental evidence regarding its effect on inflammatory cytokines in acne remains limited. This study aimed to evaluate the effect of oral bromelain administration on IL-6 levels in the tissue of acne vulgaris model rats. This *in vivo* laboratory experimental study employed a posttest-only control group design. Fifteen male Sprague-Dawley rats induced with *C. acnes* were divided into three groups: normal control (K1), negative control (K2), and treatment group (P) receiving oral bromelain at 88 mg/kgBW/day for 21 days. Tissue IL-6 levels were measured by enzyme-linked immunosorbent assay (ELISA). Data were analyzed using one-way ANOVA followed by a *post hoc* least significant difference (LSD) test. *C. acnes* induction significantly elevated tissue IL-6 levels compared to the normal control ($p<0.001$). One-way ANOVA revealed statistically significant differences in IL-6 levels between groups ($p<0.001$). The lowest IL-6 levels were observed in K1 (36.50±0.43) and the highest in K2 (94.01±0.57). The treatment group (P; 47.46±0.83) demonstrated significantly lower IL-6 levels than K2 and approximated K1 values. The *post hoc* LSD test confirmed statistically significant differences across all pairwise group comparisons ($p<0.001$). Oral bromelain administration effectively reduced IL-6 levels in the tissue of acne vulgaris model rats, demonstrating significant anti-inflammatory activity. These findings suggest that bromelain has potential as an adjunct therapy for inflammatory control in acne vulgaris.

Keywords: acne vulgaris, bromelain, interleukin-6, inflammation, Cutibacterium acnes

INTRODUCTION

Acne vulgaris is a disorder of the pilosebaceous unit characterized by pleomorphic lesions arising from hyperkeratinization of epidermal follicles, excess sebum production, *Cutibacterium acnes* activity, and immune-mediated inflammatory responses (Santer et al., 2024). *Propionibacterium acnes*, now reclassified as *Cutibacterium acnes* (*C. acnes*), is a gram-positive, anaerobic, lipophilic bacterium that colonizes the sebaceous glands of the face, chest, and back (Bergler-czop, 2020). According to data from the Global Burden of Skin Disease 2010, compiled across 187 countries, the incidence rate of acne vulgaris is approximately 9.38% of the global population; the prevalence of acne vulgaris in Indonesia was approximately 90% in 2009 (Layton et al., 2021; Ollyvia et al., 2021).

Experimental animal models, particularly acne model rats, are widely employed to elucidate the pathogenesis of inflammation and to evaluate the efficacy and safety of

therapeutic agents (Cruz et al., 2023; Kurokawa et al., 2021; Lu et al., 2026; Vasam et al., 2023). Their relatively short life cycle, ease of handling, and genetic and physiological similarities to humans allow for the modeling of cutaneous inflammatory responses that recapitulate the clinical features of acne (Rosidah et al., 2020; Chang & Grieder, 2024).

Cutibacterium acnes can trigger inflammation by secreting lipase, thereby activating an immune response that results in the production of chemokines and cytokines, including IL-1, IL-6, IL-8, and TNF-α (Bergler-czop, 2020). Keratinocytes and sebocytes are known to secrete IL-6, supporting the hypothesis that IL-6 plays a key role in the inflammatory process of acne vulgaris (Mayslich & Grange, 2021). Standard therapy for acne vulgaris aims to suppress inflammatory processes and reduce colonization of C. acnes (Cong et al., 2019; Cruz et al., 2023; Kurokawa et al., 2021; Vasam et al., 2023; Xu et al., 2025). To date, no study has evaluated the use of bromelain in acne vulgaris models, either in humans or experimental animals. Bromelain is a proteolytic enzyme derived from pineapple (Ananas comosus) and has been reported to exert anti-inflammatory effects. Research by Bakare and Owoyele (2021) demonstrated that bromelain inhibits activation of nuclear factor kappa-B (NF-κB), thereby reducing the levels of pro-inflammatory cytokines including NF-κB, IL-1, IL-6, IL-8, TNF-α, and PGE-2 in sciatic nerve tissue of Wistar rats (Bakare & Owoyele, 2021). Based on these findings, the present study aims to analyze the effect of oral bromelain administration on IL-6 levels in the tissue of acne vulgaris model rats.

This research provides several important contributions. For the advancement of medical science, this study adds to the understanding of alternative anti-inflammatory agents for acne vulgaris management, particularly regarding bromelain's role in modulating IL-6 levels in local tissue. For clinical practice, the findings may offer a potential adjunct therapy for acne patients, especially those seeking natural treatment options with fewer adverse effects than conventional therapies. For the pharmaceutical industry, this research opens opportunities for developing bromelain-based oral or topical formulations for acne treatment. For the broader community, particularly individuals with acne vulgaris, this study provides scientific evidence for the potential use of pineapple-derived bromelain as a natural alternative for managing inflammatory acne—an ingredient that is both accessible and culturally relevant in Indonesia as a major pineapple-producing country.

RESEARCH METHODS

This study is a laboratory experimental investigation employing a posttest-only control group design to assess IL-6 levels via tissue ELISA and to evaluate the role of bromelain in reducing IL-6 levels in tissue. The research was conducted at the Laboratory of the Center for Food and Nutrition Studies (*Pusat Studi Pangan dan Gizi*/PSPG), Universitas Gadjah Mada, during the period of July to September 2025. The study subjects comprised 15 male Sprague-Dawley rats, six weeks of age, with body weights ranging from 160 to 200 grams. Animals underwent a seven-day acclimatization period prior to the commencement of the study. Each treatment group consisted of five rats.

Induction of the acne model was performed by intradermal injection of *C. acnes* ATCC 11827 at a concentration of 10^9 CFU in 20 μL phosphate-buffered saline (PBS) into an area of approximately 4 cm^2 on the dorsal surface of the ear. Nodular lesions appeared two

weeks following *C. acnes* injection (Figure 1). Research subjects were subsequently randomized into three treatment groups. Group K1 (normal control) received no treatment. Group K2 (negative control) received intradermal *C. acnes* injection and oral administration of *aquades* (distilled water) at 10 ml/kgBW. Group P (treatment) received intradermal *C. acnes* injection followed by oral bromelain (2,400 GDU/g) at 88 mg/kgBW/day for 21 days. Tissue IL-6 levels were measured on day 22 using tissue ELISA according to standard laboratory protocols.

Prior to statistical analysis, data were assessed for normality using the Shapiro-Wilk test and for homogeneity of variance using the Levene test. Data satisfying assumptions of normality ($p>0.05$) and homogeneity ($p>0.05$) were analyzed using one-way ANOVA (significance threshold: $p<0.05$), followed by the *post hoc* LSD test. In the event that data were normally distributed but heterogeneous, the Welch test with *post hoc* Dunnett's T3 test would be applied. Non-normally distributed data would be analyzed using the non-parametric Kruskal-Wallis test followed by an appropriate *post hoc* procedure. This research received approval from the Research Ethics Committee

Figure 1. Acne vulgaris model rat. Visible solitary nodule (red arrow)
Source: Research Documentation, 2025

RESULTS AND DISCUSSION

RESULTS

Testing of the analysis requirements for the normality and homogeneity of the distribution of each dataset is required before performing the analysis. In this study, the normality test was carried out using the Shapiro-Wilk technique and the homogeneity of the data was tested using the Levene test. The data is normally distributed if the value is $p>0.05$ and the data has a homogeneous variant if the value is $p>0.05$. Data with normal and homogeneous distribution will use the ANOVA test and then the Post Hoc LSD test. In normal but not homogeneous data, the Welch test can be used and continued with the Post Hoc Dunnet T3 test. Data that have abnormal distribution will use the nonparametric Kruskall Wallis test and continue with the Post Data IL-6 test of the tissues in this study are normally and homogeneously distributed (**Table 1**), therefore, the comparison of tissue IL-6 levels between study groups after the intervention period (*posttest*) is analyzed using the one-way ANOVA test followed by the Post Hoc LSD test (**Table 2**).

Table 1. Normality and homogeneity test of IL-6 tissue *posttest*

	Shapiro-Wilk				Uji Levene		
	Statistik	**df**	**Nilai p**	**Remarks**	**Statistics**	**Value p**	**Remarks**
IL-6 Posttest network					2,185	0,108	Homogen
K1	0,962	4	0,821	Normal			
K2	0,951	4	0,743	Normal			
P	0,867	4	0,255	Normal			

Source: Primary Data Analysis, 2025

Remarks: K1= normal control who was not given *C. acnes* injection treatment and was not given any oral medication; K2= negative control given oral *C. acnes injection* treatment and 10 ml/kgBB of acuade; P1 = *C. acnes injection* and oral bromelain therapy 2,400 GDU/g 88 mg/KgBB; Saphiro wilk = normality test, Levene test = homogeneity test. The data meet the assumptions of normality and homogeneity if the value of p>0.05.

The mean IL-6 values of tissue between study groups at the end of the ANOVA test study also showed a statistically significant difference (p<0.001). The K1 group (normal control) had the lowest average tissue IL-6 value (36.50±0.43) and the K2 group (negative control) had the highest mean tissue IL-6 value (94.01±0.57). Group P (oral bromelain therapy) with an average (47.46±0.83) had lower levels than K2 (**Table 2** and **Figure 1**).

The differences between the study treatment groups were analyzed by conducting a Post Hoc LSD test. The results of the Post Hoc LSD test after the therapy treatment in this study resulted in a p<0.05 value for all comparisons of mean tissues between study groups. This shows that the average results between the K1, K2 and P groups each had statistically significant differences **(Table 3).**

Table 2. Differences in mouse tissue IL-6 after the intervention completion period

Groups	**N**	**IL-6 Networking**	
		Average	**±SD**
K1	5	36,50	±0,43
K2	5	94,01	±0,57
P	5	47,46	±0,83
Value p[a]		<0,001*	

Source: Primary Data Analysis, 2025

Remarks: K1= normal control who was not given *C. acnes* injection treatment and was not given any oral medication; K2= negative control given oral *C. acnes injection* treatment and 10 ml/kgBB of acuade; P = *C. acnes injection* and oral bromelain therapy 2,400 GDU/g 88 mg/KgBB; a ANOVA test *significant at p<0.05
SD: Standard deviation

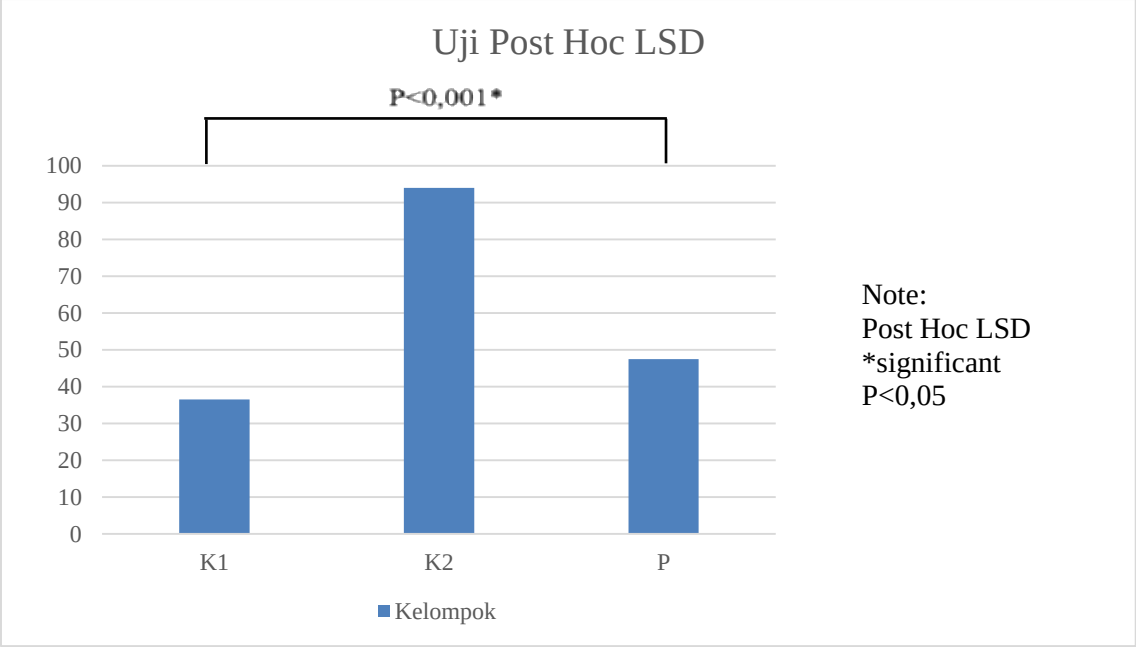

Figure 2. Differences in IL-6 tissue between groups of treatment preparations after the intervention period

Source: Primary Data Analysis, 2025

K1 = normal control who was not given *C. acnes* injection treatment and was not given any oral medication; K2= negative control given oral *C. acnes injection* treatment and 10 ml/kgBB of acuade; P1 = *C. acnes injection* and oral bromelain therapy 2,400 GDU/g 88 mg/KgBB; Post Hoc LSD Test. *Significant at p<0.05.

Table 3. Post Hoc LSD test results of tissue IL-6 levels

Groups	***Posttest***		
	Average	**Average *Diff*.**	**Value p**
K1 vs. K2	36,50±0,43 94,01±0,57	57,51	<0,001*
K1 vs. P	36,50±0,43 47,46±0,83	10,96	<0,001*
K2 vs. P	94,01±0,57 47,46±0,83	-46,56	<0,001*

Source: Primary Data Analysis, 2025

Remarks: K1= normal control who was not given *C. acnes* injection treatment and was not given any oral medication; K2= negative control given oral *C. acnes injection* treatment and 10 ml/kgBB of acuade; P = *C. acnes injection* and oral bromelain therapy 2,400 GDU/g 88 mg/KgBB; LSD Post Hoc Test; *significant at p<0.05

In the data of this study, it can be explained that the administration of oral bromelain to mice of the acne vulgaris model was proven to significantly reduce tissue IL-6 levels compared to the negative control group. Statistical analysis showed that there was a significant difference in tissue IL-6 levels between the normal, negative control and oral bromelain treatment groups (p<0.001). The results of this study can be concluded that

bromelain has the potential as an anti-inflammatory in mice model of acne vulgaris in lowering IL-6 tissue.

Acne vulgaris is an inflammatory condition in the pilosebaceous unit characterized by the activation of innate and adaptive immune responses, which is reflected in an increase in inflammatory mediators compared to skin without acne (Bergler-czop, 2020). This is in accordance with the results of this study where the levels of IL-6 in the tissues of mice injected with *C. acnes* in the negative control group showed higher IL-6 values compared to the group of mice that were not injected with *C. acnes* (normal control). This local inflammatory mechanism is caused by the activation of keratinocytes and sebocytes that produce IL-6, IL-1β and TNF-α (Huang et al., 2024; Jiang et al., 2020). Sole-administered oral bromelain (P) resulted in significantly lower tissue IL-6 levels than negative controls. These results demonstrate the ability of bromelain to suppress IL-6 levels not only systemically but also locally in tissues. This mechanism is related to bromelain's ability to modulate leukocyte infiltration and suppress NF-κB activation in epithelial cells (Bakare & Owoyele, 2021; Chakraborty et al., 2021).

Research conducted by Duarte et al. in 2022 showed the important role of herbal ingredients, including plant enzymes such as bromelain in controlling inflammation in acne through inhibition of pro-inflammatory mediators in tissues (Duarte et al., 2022). The results suggest that bromelain not only lowers IL-6 levels in the blood, but also suppresses IL-6 levels in tissues, signaling complementary systemic and local effects. Research conducted by Bakare and Owoyele in 2021 stated that bromelain was shown to lower IL-6 in nerve tissue, suggesting that the anti-inflammatory effects of bromelain are not limited to one type of tissue (Bakare & Owoyele, 2021). This reinforces the findings of this study that IL-6 levels in mouse tissues treated with oral bromelain had lower levels than IL-6 levels in mouse tissues not treated with oral bromelain. Research conducted by Savitri et al. in 2023 showed the effect of reducing local inflammation on the skin (Savitri et al., 2023). This again supports the decline of IL-6 in this research network. Based on the results of this study, the effect of the lowest decrease was in the group of mice treated with oral bromelain, it can be concluded that oral administration of bromelain can show a decrease in IL-6 levels in mouse tissue of the acne vulgaris model. These data indicate the potential of bromelain as an adjuvant agent in the inflammatory management of acne vulgaris.

CONCLUSION

Oral bromelain administration has been shown to be effective in reducing IL-6 levels in the tissue of acne vulgaris model mice. The decrease in IL-6 levels of this tissue suggests that bromelain has significant anti-inflammatory activity in the inflammatory process of acne vulgaris. Bromelain has the potential to be used as an adjunct therapy in the inflammatory control of acne vulgaris. These findings indicate that bromelain has the potential to be used as an adjunct therapy in the inflammatory control of acne vulgaris, offering a natural alternative with anti-inflammatory properties derived from pineapple. Based on these conclusions, several recommendations can be proposed. Future research should explore the optimal dosage and duration of bromelain therapy for acne vulgaris through dose-response studies to determine the most effective and safe therapeutic regimen.

Further studies are also needed to investigate the molecular mechanisms underlying bromelain's anti-inflammatory effects in acne pathogenesis more comprehensively, including its impact on other pro-inflammatory cytokines such as IL-1, IL-8, and TNF-α. Clinical trials involving human subjects with acne vulgaris are essential to validate these preclinical findings and evaluate the efficacy and safety of bromelain in clinical settings. Additionally, comparative studies between oral bromelain administration and topical bromelain formulations would be valuable to determine the most effective route of administration for acne treatment. Research on combination therapy involving bromelain with standard acne treatments could also provide insights into potential synergistic effects. For the pharmaceutical industry, there is an opportunity to develop bromelain-based pharmaceutical preparations, both oral and topical, specifically formulated for acne management. Finally, given Indonesia's position as a pineapple-producing country, further research on the utilization of local pineapple varieties as a source of bromelain for medical applications could have significant economic and public health benefits for the nation.

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