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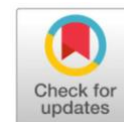
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## Original Research



***Effect of cinnamon bark (*Cinnamomum burmannii*)  
 extract cream on IL-6 and SOD Expression in a rat  
 excision wound model***



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**Abstract:** Wound healing is a complex biological process that restores tissue integrity, and disruption of this process can impair aesthetic appearance and cause psychological distress. Herbal agents such as cinnamon bark (*Cinnamomum burmannii*), known for its antioxidant, anti-inflammatory, and antibacterial properties, have potential to accelerate wound repair. This study aimed to evaluate the effect of cinnamon bark extract cream on interleukin-6 (IL-6) and superoxide dismutase (SOD) levels in rats with excision wounds. An experimental post-test only control group design was conducted using 24 male Wistar rats divided into four groups: normal rats (K1), excision wounds treated with povidone-iodine (K2), excision wounds treated with 4% cinnamon bark extract cream (K3), and excision wounds treated with 8% cinnamon bark extract cream (K4). Treatments were given for seven days, and on day eight, skin tissue samples were analyzed for IL-6 and SOD levels using the ELISA method. One-way ANOVA followed by LSD post hoc tests showed significant differences in SOD levels among groups ( $p = 0.001$ ), with the 8% cinnamon bark extract cream group ( $43.01 \pm 5.92$  ng/L) demonstrating significantly higher levels compared to other groups. In contrast, IL-6 levels showed no significant differences between groups ( $p = 0.339$ ). However, exploratory comparison suggested that the 4% cream group had the lowest mean IL-6 value ( $4.10 \pm 1.36$  ng/L) compared to povidone-iodine ( $4.74 \pm 0.60$  ng/L). Although confidence intervals crossed zero, the analysis indicated a small to moderate effect size (partial  $\eta^2 = 0.185$ ), suggesting treatment-related variability and a possible trend toward reduced inflammation in the 4% cream group. These findings suggest that topical administration of 8% cinnamon bark extract cream enhances antioxidant activity by increasing SOD levels in skin tissue after excision wounds, while the 4% cream may modestly attenuate IL-6, although further confirmatory studies are required.

**Keywords:** SOD Levels; IL-6 Levels; Cinnamon Cream; Excision Wounds.

## INTRODUCTION

Excision wounds are injuries in which the surface of the skin and underlying layers is cut to varying depths.<sup>1</sup> The healing process is an essential biological mechanism that is sometimes overlooked, involving a complex series of events aimed at restoring tissue integrity.<sup>2</sup> Impaired wound healing not only disrupts aesthetic appearance but also causes psychological distress in patients.<sup>3</sup> During this process, interleukin-6 (IL-6) functions as a key modulator of inflammatory and reparative mechanisms.<sup>4</sup> However, increased reactive oxygen species (ROS) and reduced activity of the antioxidant enzyme superoxide dismutase (SOD) can

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disrupt fibroblast function, impair neovascularization, and delay wound closure.<sup>5</sup> Wound complications must be minimized to prevent further tissue damage, patient discomfort, and microbial infection.<sup>6</sup> In clinical practice, topical povidone-iodine is commonly used, but it may cause adverse effects such as rashes, itching, swelling, or peeling.<sup>7</sup> Therefore, safe and effective herbal alternatives are needed to support wound healing.<sup>8</sup>

Cinnamon bark (*Cinnamomum burmannii*) is a natural ingredient with reported antioxidant, anti-inflammatory, and antibacterial properties.<sup>9,10</sup> Traditionally, it has been used for various therapeutic purposes, including reducing urea levels, alleviating chronic inflammation, treating liver damage, and as an antidepressant.<sup>11–13</sup> It is also a potential cosmetic ingredient due to its high flavonoid and antioxidant content.<sup>14</sup> Previous studies have demonstrated that cinnamon bark essential oil cream formulations at concentrations of 5%, 10%, and 15% meet physical and quality standards, indicating their suitability as topical preparations.<sup>15</sup> Moreover, cinnamon bark extract in a natural lip balm has been shown to accelerate lip wound healing by promoting faster wound closure.<sup>2</sup>

Despite these findings, there is limited evidence regarding the use of cinnamon bark extract in cream formulations for wound healing, particularly its effects on molecular biomarkers. SOD activity is known to decrease during wound healing, while IL-6 production rapidly increases in response to tissue injury.<sup>16, 17</sup> Although cinnamon bark extract is recognized for its antioxidant and anti-inflammatory potential, few studies have investigated its topical application in excision wound models. Specifically, there is a lack of evidence on how cinnamon bark extract cream influences IL-6, a pro-inflammatory cytokine, and SOD, a key antioxidant enzyme, during the wound healing process while other studies have been focused on oral administration or crude preparations without addressing localized dose-dependent therapeutic effects.

This highlights the need for further research on the dose-dependent effects of cinnamon bark extract cream as a topical therapy for excision wounds. Therefore, this study aimed to evaluate the effect of cinnamon bark extract cream on IL-6 and SOD levels in a rat excision wound model.

## MATERIAL AND METHOD

This research is experimental research conducted during April-May 2024 at the *Integrated Biomedical Laboratory* (IBL) of the Faculty of Medicine, Unissula Semarang. All procedures involving animals were approved by the Animal Ethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung, under clearance number 134/IV/2024/Komisi Bioetik. Material used in this study such cinnamon bark ethanol extract, aquadest, ketamine, alcohol 70%, 80%, paraffin, Fine test ELISA kit Rat IL-6. (BT LAB, China; Cat. No. E2105Ra for IL-6, Cat.), A post-test only control group design was used with 28 male Wistar rats (*Rattus norvegicus*), aged 2–3 months and weighing 190–210 g. The animals were randomly divided into four groups (n = 6): healthy control without wounds (K1), excision wound treated with povidone-iodine (K2), excision wound treated with 4% cinnamon bark extract cream (K3), and excision wound treated with 8% cinnamon bark extract cream (K4). Treatments were administered once daily for seven days. On day eight, skin tissue samples were collected for biochemical analysis.

### Cinnamon Bark Extract Preparation

Cinnamon bark (*Cinnamomum burmannii*) was dried at 40°C, ground into powder, and sieved (20 mesh). A total of 450 g of powder was extracted by maceration using 70% ethanol (1,500 mL) for 3 days with occasional stirring, filtered, and remacerated twice. The filtrate was concentrated using a rotary evaporator at 40°C to obtain a thick extract.

### Cream Formulation

The vanishing cream base was prepared from stearic acid, triethanolamine, glycerin, borax, and distilled water. Cinnamon bark extract was incorporated into the base to obtain 4% and 8% formulations, which were homogenized and stored in sterile containers until use.

### Wound Induction and Treatment

The research subjects were 24 male rats of the *Wistar* strain (*Rattus norvegicus*), 2-3 months old, with a body weight of 190-210 grams, which were divided into 4 groups, each amounting to 6 rats. The mice that had been adapted for 7 days were anesthetized with a mixture of ketamine (60 mg/kg BW) and xylazine (20mg/kg BW), the surface of the skin that had been cleaned using bovidon iodine to avoid infection during wound making. The wound was made using a circular *biopsy punch* with a full thickness of 6 mm. The next day, the rats were then given treatment according to their group. Topical treatment was given once a day for 7 days after UV B irradiation. While skin samples validation is do visually

### Cinnamon Bark Extract Cream Formulation

Prepare the *vanishing cream* in 50 grams with the composition (*Stearate acid, Triethanolamine, Glycerin, Borax, and aquadest*). Heat the water in a bekglas, then put 14.5 grams of stearate acid in a porcelain cup and place it on top of boiling water, stir until it melts. Add Borax 125mg in sequence then homogenize, add Triethanolamine 1.5 ml, Glycerine 10 ml, and aquadest 25ml until well mixed. The cream in 20 grams is done by weighing 0.6 grams of sweet peel extract then put in a mortar, adding enough Tween to be homogenized. Add 20 grams of vanishing cream, mix well until homogeneous, put the cinnamon extract to the pot.<sup>18</sup>

### Tissue Sampling

After the treatment, on the 8th day, a tissue was taken. Previously, all *Wistar* rats were humanely euthanized under anesthesia prior to tissue collection. Make a tissue incision in the injured part of the skin, using sterile scissors and tweezers. The tissue sample was cut and weighed, then the tissue was added with PBS (pH 7.4). Tissue samples are homogenized in cold conditions, 4°C. Then it is centrifuge at 2000-3000 rpm, for 20 minutes. Then supernatants or centrifugation substances that have a lower specific weight are taken and used as test samples. If the sample will be stored first, then the sample can be stored at a temperature of -20°C.

### Measurement of IL-6 and SOD Levels

The skin tissue samples that had been obtained were then analyzed for SOD and IL-6 levels using commercial ELISA kits (BT LAB, Biotechnology Laboratory, China; Rat IL-6 ELISA Kit Cat. No. E0135Ra, and Rat SOD ELISA Kit Cat. No. E0168Ra). Procedures followed the manufacturer's instructions. Absorbance was measured at 450 nm using a microplate reader (Bio-Rad, USA), and all measurements were performed in duplicate. The intra- and inter-assay coefficients of variation were below 10%.

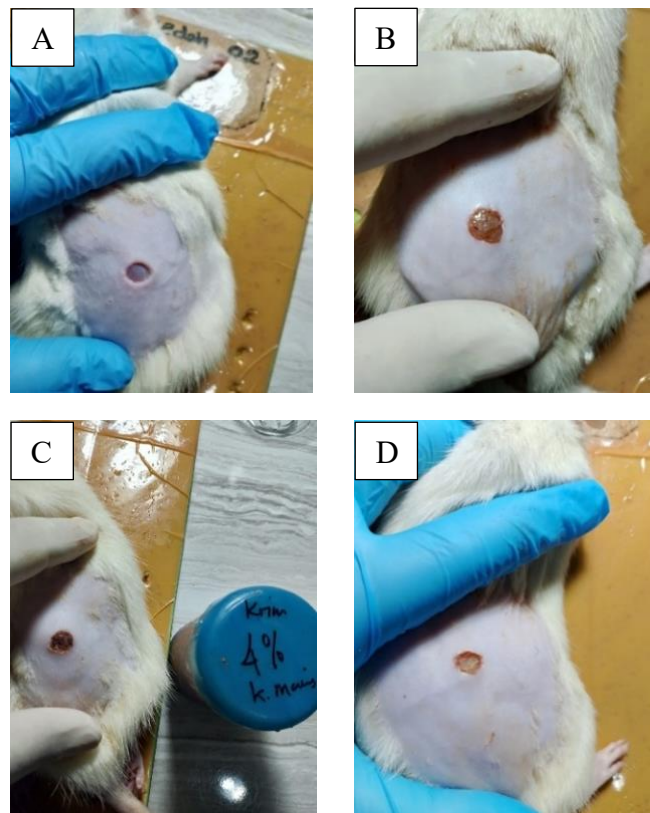
### Statistical Analysis

All data then statistically analyses, all data were expressed as mean  $\pm$  standard deviation (SD). Normality was tested with the Shapiro-Wilk test, and

group differences were analyzed using one-way ANOVA followed by least significant difference (LSD) post hoc tests. A  $p$ -value  $< 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

## RESULTS AND DISCUSSION

Macroscopic images in rat subjects with excision wound models showed accelerated wound healing and closing, in the excision wound group given a dose of cinnamon bark extract cream at a dose of 8% showed the best results macroscopic compared to the cinnamon bark extract cream treatment group at a dose of 4%, as well as the povidone iodine group. as shown in figure 1.



**Figure 1.** Comparison of rat skin after excision wound on day 7, (A) Untreated control. (B) Positive control treated with povidone-iodine 10%. (C) Excision wound treated with cinnamon bark extract cream (KEKKM) 4%. (D) Excision wound treated with cinnamon bark extract cream (KEKKM) 8%. Images were obtained at the same distance and under identical lighting; scale bars = 5 mm. Representative rats are shown (Wistar rats,  $n = X$  per group). Abbreviation: KEKKM, krim ekstrak kulit kayu manis (bark extract cream).

**Table 1.** Mean IL-6 Levels, Normality Test, Homogeneity Test, and One-Way ANOVA Results Across Treatment Groups

Group	Healthy rats (K1)	Povidone-iodine (K2)	KEKKM 4% (K3)	KEKKM 8% (K4)	$p$ value
Mean	4.59	4.74	4.10	5.41	
SD	0.98	0.60	1.36	1.31	
Shapiro wilk	0.566*	0.412*	0.145*	0.560*	
Levene's Test					0.647*
One way anova					0.339

Description :

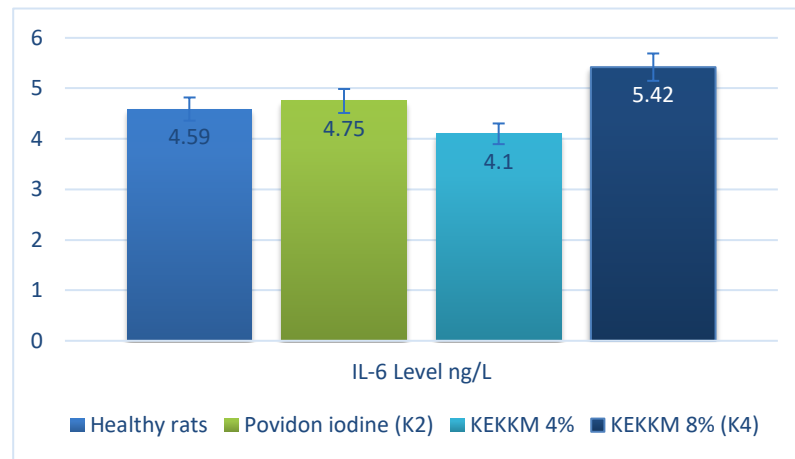
\*Uji Saphiro Wilk ( $p > 0.05$  = normal)

\*Levene's Test ( $p > 0.05$  = homogen)

\*One way anova ( $p < 0.05$  = significance)

Based on the results of the study in table 1 and figure 2, the average IL-6 level in the healthy rat group (K1) was 4.59 ng/L  $\pm$  0.98, the average group of *Povidone-iodine* (K2) was 4.74 ng/L  $\pm$  0.60, the average group (KEKKM) of cinnamon bark extract cream with a dose of 4% (K2) was 4.10 ng/L  $\pm$  1.36 and the average group (KEKKM) of cinnamon bark extract cream with a dose of 3% (K3) was 4.10 ng/L  $\pm$  1.36.

The distribution and average variant of IL-6 levels showed that the results were normally distributed with *the Shapiro Wilk* test with a value of  $p > 0.05$  and had a homogeneous data variant with the results of *the Levene's Test* with a value of  $p = 0.647$  ( $p > 0.05$ ). The average results of normal and homogeneous IL-6 levels were followed by conducting a *one-way anova test*.



**Figure 2.** Mean IL-6 levels between treatment groups

One-way ANOVA showed no significant differences among groups,  $F(3,16) = 1.21$ ,  $p = 0.339$ , with a small-to-moderate effect size (partial  $\eta^2 = 0.185$ ). Post-hoc LSD tests confirmed no significant pairwise differences (all  $p > 0.05$ ).

Although no significant differences were detected ( $F(3,16) = 1.21$ ,  $p = 0.339$ ), a small-to-moderate effect size was observed (partial  $\eta^2 = 0.185$ ), suggesting that treatment may account for some variability in IL-6 levels. Confidence intervals included zero, indicating statistical uncertainty, but the distribution of means showed a potentially favorable trend in the 4% cream group (K3), which exhibited a 13.5% reduction in IL-6 compared to povidone-iodine (K2). By contrast, the 8% cream group (K4) showed higher IL-6 levels than all groups (31.9% higher than K3, 17.4% higher than K2).

**Table 2.** Mean SOD levels, normality and homogeneity and *one-way anova test* between treatment groups

Group	Healthy rats (K1)	Povidone-iodine (K2)	KEKKM 4 (K3)	KEKKM 8% (K4)	p value
Mean	27.83	23.31	25.32	43.01	
SD	2.72	6.08	5.87	5.92	
Shapiro wilk	0.171*	0.105*	0.745*	0.073*	
Levene's Test					0.308*
One way anova					0.001*

Description :

\**Uji Saphiro Wilk* ( $p > 0.05$  = normal)

\**Levene's Test* ( $p > 0.05$  = homogen)

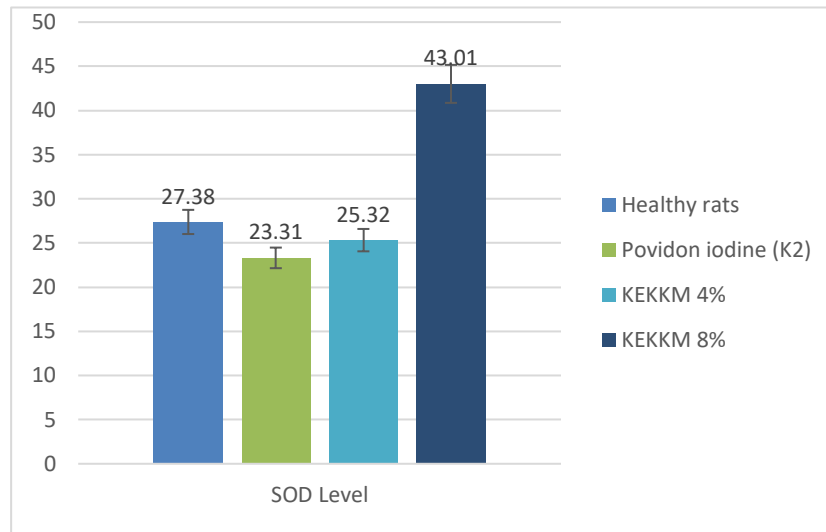
\**One way anova* ( $p < 0.05$  = significance)

Based on the results of the study in table 2 and graph 3, the average SOD level in the healthy rat group (K1) was 27.83 ng/L  $\pm$  2.72, the average of *the*



*Povidone-iodine* (K2) group was  $23.31 \text{ ng/L} \pm 6.08$ , the average group (KEKKM) of cinnamon bark extract cream with a dose of 4% (K2) was  $25.32 \text{ ng/L} \pm 5.87$  and the average group (KEKKM) of cinnamon bark extract cream with a dose of 8% (K4) was  $43.01 \text{ ng/L} \pm 5.92$ .

The results of the average data on SOD levels in the four groups were normally distributed with a *Shapiro Wilk test value* of  $p > 0.05$  and had a homogeneous data variant with the results of *the Levene's Test* with a value of  $p = 0.308$  ( $p > 0.05$ ). It was concluded that the results of normal distributed data and homogeneous data variants.



**Figure 3.** TGF- $\beta$  levels between groups

Statistical analysis with *the One-Way Anova test* obtained a value of  $p = 0.001$  ( $p < 0.05$ ) so that it was concluded that there was a significant difference in the average SOD level between the treatment groups. The *significant results of the One Way Anova test* were followed by *the Post Hoc LSD test* to determine the dosage group of cinnamon bark extract cream that had the most effect on the condition of excision wounds, shown in table 3 below.

**Table 1.** *Post Hoc LSD Test* SOD Levels in Each Group

Group	Comparison Group	Sig.
Healthy rats	<i>Povidon iodine</i>	0.199
	KEKKM 4%	0.468
	KEKKM 8%	*0.000
<i>Povidon iodine</i>	Healthy rats	0.199
	KEKKM 4%	0.559
	KEKKM 8%	*0.000
KEKKM 4%	Healthy rats	0.468
	<i>Povidon iodine</i>	0.559
	KEKKM 8%	*0.000
KEKKM 8%	Healthy rats	*0.000
	<i>Povidon iodine</i>	*0.000
	KEKKM 4%	*0.000

The \* sign indicates different groups of meanings.

One-way ANOVA demonstrated a significant treatment effect,  $F(3,16) = 12.64$ ,  $p = 0.001$ , with a large effect size (partial  $\eta^2 = 0.703$ ). Post-hoc LSD tests revealed that the 8% cream group (K4) had significantly higher SOD levels compared to all other groups ( $p < 0.001$  for each comparison).

Relative to povidone-iodine (K2), SOD levels in the 8% cream group (K4) increased by 83.4% (43.01 vs. 23.31 ng/L). Compared to the 4% cream group (K3), the increase was 70.0%, and compared to healthy controls (K1), 54.6%.

Wound healing is a dynamic process that progresses through overlapping phases of inflammation, proliferation, and remodeling.<sup>19, 20</sup> The inflammatory phase is critical for hemostasis and early defense against microbial invasion and must be tightly regulated to enable transition toward tissue repair.<sup>21</sup> IL-6 is a key modulator in this process, coordinating leukocyte activation, fibroblast proliferation, and the switch from pro-inflammatory to reparative signaling.<sup>22</sup> Additional insights into IL-6's dual role in wound repair and fibrosis are reported by Johnson et al. in *Biomedicines* 2020, specifically emphasizing how dysregulated IL-6/TGF- $\beta$  signaling can lead to impaired healing or scarring.<sup>22</sup>

In this study, administration of cinnamon bark extract cream did not result in significant differences in IL-6 levels between groups. This outcome may be related to the timing of measurement on Day 8, which is beyond the acute inflammatory phase (typically Days 1–3). Several studies have shown that IL-6 expression peaks rapidly after injury and declines during the remodeling phase, making it less suitable as a late-phase biomarker of inflammation.<sup>23–25</sup> This is consistent with the broader understanding that inflammatory cytokines such as IL-6 dominate early phases but diminish as repair progresses.<sup>26</sup> Although the differences were not statistically significant, exploratory analysis revealed that the 4% cream group exhibited the lowest mean IL-6 level ( $4.10 \pm 1.36$  ng/L), about 13.5% lower than povidone-iodine, whereas the 8% cream group showed higher IL-6 values compared to all groups. These results suggest that lower-dose cinnamon cream may have a modest anti-inflammatory effect, while higher doses might sustain inflammatory signaling. Nonetheless, because these findings were not statistically significant, they should be considered exploratory and require confirmation with time-series studies including earlier sampling points (Day 1–3).

In contrast, SOD levels showed a significant increase in the 8% cinnamon bark extract cream group compared to all other groups. SOD is a primary endogenous antioxidant that catalyzes the dismutation of superoxide radicals into hydrogen peroxide and oxygen, thereby limiting ROS-mediated tissue damage during wound repair.<sup>27, 28</sup> The elevated SOD levels observed in the 8% group indicate enhanced antioxidant capacity, which is consistent with accelerated tissue regeneration. The high flavonoid content of cinnamon bark extract likely contributes to this effect through free radical scavenging and upregulation of endogenous antioxidant enzymes.<sup>10,13</sup> Similar findings have been reported by Fadilah et al. (2023), who demonstrated that curcumin-based hydrogels improved wound healing by increasing SOD activity and reducing ROS burden.<sup>29</sup> Another relevant study using cinnamon extract in a gastric ulcer model reported increased SOD-1 expression and reduced TNF- $\alpha$  levels, supporting cinnamon's antioxidant and anti-inflammatory effects in tissue repair contexts.<sup>30</sup>

Taken together, these results suggest that cinnamon bark extract cream has dose-dependent biological effects: an 8% formulation enhances antioxidant defense via SOD upregulation, while a 4% formulation may modestly modulate inflammatory cytokines such as IL-6. Regardless this study has several limitations. First, the sample size was relatively small ( $n = 6$  per group), which may reduce statistical power. Second, IL-6 was only measured on Day 8, potentially missing peak inflammatory responses that occur earlier in wound healing. A time-series design with multiple sampling points (e.g., Days 1–3 and Day 7) would provide a clearer picture of cytokine dynamics. Third, the study relied primarily on biochemical assays (IL-6 and SOD) without histological or molecular confirmation of tissue regeneration. Finally, the absence of a true negative wound control group limits the ability to isolate the specific contribution of cinnamon bark extract compared to natural healing. Future studies should address these issues to strengthen the evidence for dose optimization and mechanistic pathways.

## CONCLUSION

Topical administration of cinnamon bark extract cream (*Cinnamomum burmannii*) did not significantly alter IL-6 levels in excision wounds, although exploratory trends suggested that the 4% formulation modestly reduced IL-6 compared to povidone-iodine, whereas the 8% formulation showed higher values. By contrast, the 8% cream significantly increased SOD levels, indicating enhanced antioxidant activity that may contribute to improved tissue regeneration. These findings suggest that cinnamon bark extract cream exerts dose-dependent effects, with higher concentrations promoting antioxidant defense and lower concentrations potentially modulating inflammatory responses. Topical application of 8% cinnamon bark extract cream therefore shows promise as a natural antioxidant agent for supporting wound healing, though further studies with larger sample sizes, time-series cytokine analyses, and clinical models are needed to determine optimal dosing and therapeutic applicability.

## AUTHORS' CONTRIBUTIONS

*Erika Hidayati*: Data curation, Visualization, Investigation, Writing-Original draft; *Chodidjah*: Supervision, Conceptualization, Reviewing; *Titiek Sumarawati*: Supervision, Reviewing, Validation.

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## DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

## DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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