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THE EFFICACY OF AN ETHANOLIC EXTRACT GEL OF *AVERRHOA BILIMBI LINN.* ON THE HEALING OF TRAUMATIC ORAL MUCOSAL ULCERS IN WISTAR RATS

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ABSTRACT

Star fruit (*Averrhoa bilimbi Linn*.) contains flavonoids, tannins, saponins, and triterpenoids that contribute to wound healing. Flavonoids act as antioxidants, tannins reduce inflammation, saponins stimulate collagen formation, and triterpenoids support tissue regeneration. This study aimed to compare the effectiveness of 10% and 20% ethanolic extracts of belimbing wuluh in influencing superoxide dismutase (SOD) and malondialdehyde (MDA) expression as well as fibroblast count in traumatic ulcers. An in vivo experimental design with a post-test only control group was conducted on male Wistar rats for 5 days. Subjects were divided into five groups: standard control, negative control (placebo), positive control (0.1% triamcinolone acetonide), treatment I (10% gel extract), and treatment II (20% gel extract). Kruskal–Wallis analysis showed significant differences among groups ($p = 0.0001$) for all parameters. The Mann–Whitney post hoc test indicated significant differences between the treatment and control groups, with $p = 0.002$ in most comparisons. The 20% concentration resulted in higher increases in SOD expression and fibroblast numbers, and greater reductions in MDA levels compared to the 10% concentration. Therefore, the ethanolic gel extract of belimbing wuluh is effective as an antioxidant in promoting the healing of traumatic ulcers, particularly through the activity of flavonoids as free radical scavengers and stimulators of fibroblast proliferation.

Kata Kunci:

Ulkus traumatik;
Belimbing wuluh;
Averrhoa bilimbi Linn;
Antioksidan

ABSTRAK

Buah belimbing wuluh (*Averrhoa bilimbi Linn.)* mengandung flavonoid, tanin, saponin, dan triterpenoid yang mendukung penyembuhan luka. Flavonoid berperan sebagai antioksidan, tanin mengurangi inflamasi, saponin merangsang kolagen, dan triterpenoid membantu regenerasi jaringan. Penelitian ini bertujuan membandingkan efektivitas ekstrak etanol belimbing wuluh konsentrasi 10% dan 20% terhadap ekspresi superoxide dismutase (SOD), malondialdehyde (MDA), dan jumlah fibroblas pada ulkus traumatik. Desain penelitian menggunakan metode eksperimental in vivo dengan post-test only control group pada tikus wistar jantan selama 5 hari. Subjek dibagi menjadi lima kelompok: kontrol standar, kontrol negatif (plasebo), kontrol positif (triamcinolone acetonide 0,1%), perlakuan I (ekstrak gel 10%), dan perlakuan II (ekstrak gel 20%). Analisis Kruskal-Wallis menunjukkan perbedaan bermakna antar kelompok (p=0.0001) pada semua parameter. Uji lanjut Mann-Whitney memperlihatkan perbedaan signifikan pada kelompok perlakuan dibanding kontrol, dengan p=0.002 pada sebagian besar perbandingan. Konsentrasi 20% menunjukkan peningkatan SOD dan fibroblas serta penurunan MDA lebih besar dibanding konsentrasi 10%. Dengan demikian, ekstrak gel etanol belimbing wuluh efektif sebagai antioksidan dalam mendukung penyembuhan ulkus traumatik, terutama melalui aktivitas flavonoid sebagai penangkap radikal bebas dan stimulator proliferasi fibroblas.

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INTRODUCTION

Oral ulcers are among the most common conditions affecting the oral mucosa (Babu et al., 2017). Acute oral ulcers are usually painful and persist for less than two weeks, whereas chronic oral ulcers may last longer than two weeks (Minhas et al., 2019). The etiology of oral ulcers is generally influenced by environmental factors such as mechanical trauma, smoking habits, and fatigue (Iris et al., 2018), as well as dietary factors that irritate the oral mucosa and trigger ulcer formation (Jain et al., 2020). The etiology and pathogenesis of traumatic oral ulcers are varied and complex (Thakrar & Chaudhry, 2016), and can be classified into four categories: infection, immune disease, trauma, and neoplastic causes (Fitzpatrick et al.,

2019). Traumatic factors may include sharp teeth or ill-fitting dentures located near the ulcer site (Parajuli & Maharjan, 2017).

Triamcinolone acetonide (TA) is a corticosteroid derived from prednisolone with moderate to high potency. It is available in topical forms such as cream (0.1%) and ointment (0.1%), commonly prescribed by healthcare providers (Ofluoglu et al., 2017). Triamcinolone acetonide is frequently used for its anti-inflammatory effects (Kavita et al., 2020) and can reduce pain caused by traumatic irritation (Mustafa et al., 2018). Its mechanism of action includes inhibition of granulation tissue formation, phagocytosis, prostaglandin and leukotriene synthesis, as well as suppression of cellular immunity (Singh et al., 2018). However, long-term use of topical corticosteroids and antibiotics may cause fungal infections and antibiotic resistance, potentially leading to severe or even life-threatening side effects (Casale et al., 2017).

Natural plant-based compounds have been increasingly explored as alternative treatments for traumatic wounds. Ethanol extract of papaya leaves (*Carica papaya* L.), for instance, has been shown to accelerate the healing of traumatic wounds in the buccal mucosa of Wistar rats (Femilian et al., 2019). Another promising plant is star fruit (*Averrhoa bilimbi* Linn.), which is widely distributed in tropical regions such as Indonesia, Malaysia, Thailand, Cambodia, and the Philippines (Sutjaritvorakul & Chutipaijit, 2020). Pharmacologically, *A. bilimbi* possesses diverse activities, including antibacterial, antidiabetic, antihypertensive, antithrombotic, hypolipidemic, hepatoprotective, cytotoxic, antifungal, and wound-healing properties (Lakshmiprabha et al., 2020). Of particular relevance to oral ulcer healing are its antioxidant, wound-healing, and anti-inflammatory effects. The bioactive compounds in star fruit—flavonoids, tannins, saponins, and triterpenoids—play a central role in these processes: flavonoids act as antioxidants that neutralize free radicals, tannins exert anti-inflammatory effects, saponins stimulate collagen formation, and triterpenoids promote tissue regeneration (Dewi et al., 2019). These properties highlight the potential of star fruit as an alternative therapy to accelerate oral mucosal wound healing.

Star fruit also has a high total phenolic content (TPC), which contributes to its antioxidant capacity (Anuar & Salleh, 2019). Phenolic compounds such as phenolic acids, flavonoids, and tannins are major plant constituents responsible for antioxidant effects (Rosli et al., 2018). Plants with antioxidant activity contain both enzymatic and non-enzymatic components that contribute to reducing reactive oxygen species (ROS) production (Akyol et al., 2020).

In wound healing, excessive ROS generation at the injury site can disrupt the antioxidant balance, thereby delaying tissue repair (Zhang et al., 2020). Lipid peroxidation is one of the major consequences of ROS activity, and malondialdehyde (MDA) is a widely recognized marker of lipid peroxidation (LPO) and oxidative stress in various pathological conditions (Bilgen et al., 2019). Antioxidants can decrease MDA levels while enhancing superoxide dismutase (SOD) activity in plasma and tissues (I'tishom & Sudjarwo, 2020). This study aims to compare the effectiveness of 10% and 20% ethanol extracts of star fruit (*Averrhoa bilimbi Linn.*) in healing traumatic oral ulcers. The choice of these concentrations is important to identify the optimal dose for enhancing antioxidant activity, reducing oxidative stress, and accelerating tissue regeneration. It is hypothesized that the 20% concentration will demonstrate higher efficacy compared to the 10% concentration. The findings of this study are expected to provide scientific evidence for the use of natural-based therapies in traumatic ulcer healing and further support the pharmacological potential of *A. bilimbi* as an antioxidant and wound-healing agent.

METHOD

Type of Research

This study was an in vivo experimental study with a post-test only control group design using test animals (Damayanti et al., 2021). This research was conducted in October – November 2021.

Population and Sample

The experimental animals used were male Wistar rats aged ±12 weeks, weighing 200–250 grams, healthy, and walking normally. A total of 40 rats were randomly assigned (simple randomization) into five groups (n=8 each):

1. Standard group: healthy rats without traumatic ulcer induction. Data from this group were not presented in the analysis because the focus of the study was on treatment comparisons.
2. Negative control: traumatic ulcers + placebo (gel without extract).
3. Positive control: traumatic ulcers + triamcinolone acetonide 0.1%.

4. Treatment I: traumatic ulcers + 10% belimbing wuluh gel extract.
5. Treatment II: traumatic ulcers + 20% belimbing wuluh gel extract.

All procedures involving animals received ethical approval from the University Animal Research Ethics Committee, ensuring compliance with applicable animal research standards and guaranteeing the welfare and humane treatment of the Wistar rats throughout the study.

Data Collection

The analysis of bioactive compounds in star fruit extract was carried out using GC-MS (Thermo GC-Trace Ultra VER: 5.0, Bremen, Germany) with DSQ II 70 eV electron ionization mass spectroscopy. The column temperature was set at 80–250°C with a heating rate of 8°C/minute, while injector and MS transfer temperatures were 280°C and 290°C, respectively. Helium gas was used as the carrier at a flow rate of 1.0 mL/min with a sample volume of 1 mL, allowing identification of the main extract compounds based on retention time and mass (Suluvoy & Berlin Grace, 2017).

Traumatic ulcers were induced on the left buccal mucosa of Wistar rats using a sterile 12 × 12 mm needle with a plus (+) pattern after intraperitoneal anesthesia with ketamine hydrochloride (75 mg/kg BW) and xylazine (5 mg/kg BW) (Akbas et al., 2019). Topical treatment was given once daily for five days: the treatment groups received 10% and 20% star fruit gel extracts, the positive control received 0.1% triamcinolone acetonide, and the negative control received a gel base without extract.

On day five, ulcer tissue was collected for histopathological and biochemical analysis. Histopathology was performed using Hematoxylin–Eosin staining, and fibroblasts were observed under a light microscope at 400× magnification (Deyhimi et al., 2016). Antioxidant activity was assessed by measuring SOD and MDA levels using a commercial ELISA kit (Elk Biotechnology, China) according to the manufacturer's protocol.

Data Analysis and Processing

Data were analyzed using SPSS version 22. Normality was tested with the Shapiro–Wilk test and homogeneity with the Levene test. SOD and MDA levels in oral mucosal ulcers were presented in tabular form, including their distribution. Antioxidant enzyme levels and MDA levels were analyzed with One-Way ANOVA. If differences among treatments were found, analysis was continued with the Tukey HSD post hoc test. If the data were not normally distributed, the Kruskal–Wallis test was applied as an alternative..

RESULT

The results of an experimental study with a post-test only control group design in male Wistar rats over five days are presented in detail in tables and figures to facilitate understanding of the effects of star fruit extract on antioxidant activity, oxidative damage levels, and fibroblast proliferation in traumatic buccal mucosal ulcers.

Figure 1. Histopathology of rat mucosal wound tissue stained with Hematoxylin–Eosin at 10×40 magnification. Image A shows the negative control group with relatively low fibroblast density. Image B shows the positive control group treated with 0.1% triamcinolone acetonide, with an increase in fibroblast count compared to the negative control. Image C shows treatment group I with 10% belimbing wuluh extract, exhibiting moderate fibroblast density. Image D shows treatment group II with 20% belimbing wuluh extract, showing the highest fibroblast count among all groups, indicating more optimal fibroblast proliferation.

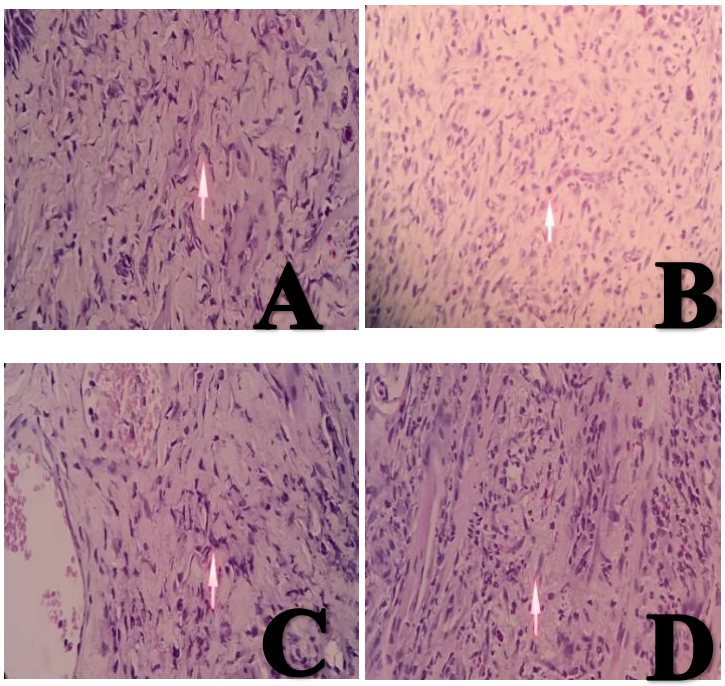

Figure 1.

Table 1 below shows the main compounds detected in ethanol extracts of star fruit (*Averrhoa bilimbi Linn.)* using Gas Chromatography-Mass Spectroscopy (GC-MS).

Table 1. Results of *Averrhoa bilimbi Linn*. ethanol extract using Gas Chromatography–Mass Spectroscopy (GC-MS)

Sample	Solvent	Injecting volume(µl)	Substance detected	Retention Time (min)
Wuluh star fruit	Ethanol	10	Decanoic acid	6. 301
			Dodecanoic acid	7. 964
			Hexadecanoic acid	10. 845

The analysis results show that the ethanol extract of star fruit contains several major saturated and unsaturated fatty acids, namely decanoic acid, dodecanoic acid, and hexadecanoic acid, with retention times of 6.301, 7.964, and 10.845 minutes, respectively. These compounds are known to have antioxidant properties and may play a role in wound healing and inflammation modulation, thereby supporting the potential of star fruit as a therapeutic agent for traumatic mucosal ulcers. After determining the bioactive compounds contained in the extract of star fruit (*Averrhoa bilimbi Linn*.), the next step was to analyze its effects on antioxidant activity, oxidative stress, and fibroblast proliferation in oral mucosal ulcers in Wistar rats. The results in Table 2 show significant differences among groups in all parameters analyzed, namely SOD, MDA, and fibroblast count.

The results in Table 2 show differences in SOD, MDA, and fibroblast counts across all study groups. After statistical analysis using the Kruskal–Wallis test, p-values < 0.05 were obtained for all parameters, indicating significant differences among groups. For the SOD parameter, the 20% treatment group showed the highest antioxidant activity (4.16 ± 1.87), followed by the 10% treatment group (1.80 ± 0.42), the positive control (1.14 ± 0.10), and the lowest in the negative control (0.71 ± 0.24). This indicates that a higher extract concentration is associated with increased SOD activity.

For the MDA parameter, an indicator of oxidative stress, the 20% treatment group showed the greatest reduction in MDA levels (4.70 ± 2.99) compared to the 10% group (12.4 ± 1.71), the positive control (25.1 ± 2.52), and the highest negative control (39.8 ± 12.8). These findings demonstrate that star fruit extract can reduce oxidative damage in ulcer tissue.

Table 2. Differences in the Mean SOD, MDA, and Fibroblast Counts Across Groups

Treatment Group	Mean ± SD	Significance Level (p-value)
SOD		
Star fruit wuluh concentration 10%	1.80 ± 0.42	
Star fruit wuluh concentration 20%	4.16 ± 1.87	0.0001*
Control +	1.14 ± 0.10	
Control –	0.71 ± 0.24	
MDA		
Star fruit wuluh concentration 10%	12.4 ± 1.71	
Star fruit wuluh concentration 20%	4.70 ± 2.99	0.0001*
Control +	25.1 ± 2.52	
Control –	39.8 ± 12.8	
Fibroblasts		
Star fruit wuluh concentration 10%	194.4 ± 25.4	
Star fruit wuluh concentration 20%	234.0 ± 11.8	0.0001*
Control +	220.0 ± 4.09	
Control –	176.6 ± 29.5	

significance $p<0.05$, Kruskal Wallis statistic test

Meanwhile, for fibroblast counts, the 20% treatment group again showed the highest value (234.0 ± 11.8), followed by the 10% group (194.4 ± 25.4), the positive control (220.0 ± 4.09), and the negative control (176.6 ± 29.5). This suggests that belimbing wuluh extract can stimulate fibroblast proliferation, which plays an important role in wound healing. In conclusion, these results demonstrate a dose–response relationship, with the 20% star fruit extract concentration showing stronger antioxidant effects, greater reduction in oxidative stress, and enhanced fibroblast proliferation compared to the 10% concentration and the controls.

Table 3 shows the results of post hoc analysis using the Mann–Whitney test. For SOD, significant differences were found between the 10% and 20% treatment groups ($p = 0.002$), and between the 10% group and the positive control ($p = 0.025$). Other comparisons, including 20% extract versus both control groups, also showed significant differences ($p < 0.05$). These results confirm that increasing the concentration of star fruit extract significantly enhances SOD antioxidant activity compared to the control. For the MDA parameter, all comparisons showed significant differences ($p = 0.002$), indicating that star fruit extract significantly reduced MDA levels, with the optimal effect at 20%. For fibroblast counts, significant differences were observed between the 10% and 20% treatment groups ($p = 0.002$) and between the 20% treatment group and the negative control ($p = 0.004$). However, no significant difference was found between the 20% treatment group and the positive control ($p = 0.141$), indicating that fibroblast proliferation with 20% extract was nearly equivalent to that in the positive control group. Based on these findings, star fruit extract significantly increased antioxidant activity, reduced oxidative stress, and stimulated fibroblast proliferation, with the 20% concentration producing more optimal effects than the 10% concentration.

Table 3. Follow-up Test The Differences in Mean SOD, MDA, Fibroblasts, Inflammation Expression Between Groups

Treatment Group		Significance Level (p-value)
SOD		
Star fruit wuluh concentration 10%	Star fruit wuluh concentration 20%	0.002*
	Control +	0.025*
	Control –	0.002*
Star fruit wuluh concentration 20%	Control +	0.002*
	Control –	0.002*
Control +	Control –	0.002*
MDA		
Star fruit wuluh concentration 10%	Star fruit wuluh concentration 20%	0.002*
	Control +	0.002*
	Control –	0.002*
Star fruit wuluh concentration 20%	Control +	0.002*
	Control –	0.002*
Control +	Control –	0.002*
Fibroblasts		
Star fruit wuluh concentration 10%	Star fruit wuluh concentration 20%	0.002*
	Control +	0.009*
	Control –	0.141*
Star fruit wuluh concentration 20%	Control +	0.004*
	Control –	0.002*
Control +	Control –	0.002*

*significance $p<0.05$, Mann Whitney statistical test

DISCUSSION

Wuluh (*Averrhoa bilimbi Linn.)* is one of the plants widely used by the Indonesian people. Starfruit contains many beneficial active compounds, such as flavonoids, tannins, and phenols, which can play an important role as antioxidants (Arifin & Jumal, 2020). Wuluh star fruit has been reported to possess relevant antioxidant and antidiabetic properties (Ahmed et al., 2018). The highest natural flavonoid content is found in many fruits, vegetables, flowers, and grains (Dias et al., 2021). Wuluh star fruit is a fruit known to be rich in antioxidants, which have been tested through in vitro and in vivo analyses (Chau et al., 2023). Plants containing flavonoid compounds have antioxidant, antibacterial, antiviral, anti-inflammatory, anti-allergic, and anticancer properties (Septiyan et al., 2021).

Hexadecanoic acid, also known as palmitic acid, is the most common saturated fatty acid found in animals, plants, and microbes (Yu et al., 2020). This compound has antimicrobial, antifungal, anti-inflammatory, and antioxidant properties (Muniandy et al., 2018). GC-MS analysis shows that hexadecanoic acid is present in the form of esters in the extract, which may play a key role in its antioxidant and antimicrobial activity (Irawan et al., 2017). Wuluh star fruit also contains bioactive compounds such as flavonoids. These compounds can prevent the harmful effects of free radicals by acting as antagonists, directly inhibiting them and breaking down hydrogen peroxide (H_2O_2) into peroxyl radicals (OOH) (Solfaine et al., 2021).

Antioxidants can minimize oral cavity injuries by reducing inflammatory processes, regulating excessive protease activity, and suppressing ROS-induced neutrophil accumulation at the injury site (Sarkar et al., 2020). In vitro antioxidant activity of star fruit extract has been shown to inhibit intracellular ROS (Francis & Nayak, 2017). Flavonoids reduce oxidative stress by increasing the antioxidant capacity of superoxide dismutase (SOD) and lowering malondialdehyde (MDA) levels as an oxidative stress marker

(Jian et al., 2018). Incision wounds in experimental animals also showed improved healing after antioxidant administration, with increased levels of SOD and catalase as key antioxidant enzymes (Qadir et al., 2021). In this study, statistical analysis using the Kruskal-Wallis test showed significant differences in SOD expression across all groups ($p = 0.0001$). Treatment group II (20% extract) demonstrated the highest increase in SOD activity (mean 4.16 ± 1.87), compared to group I (10% extract, mean 1.80 ± 0.42). A post-hoc Mann-Whitney test revealed $p = 0.002$ between the two treatment groups, confirming that higher extract concentrations significantly enhance SOD antioxidant activity. These results suggest that flavonoids and triterpenoids in belimbing wuluh contribute to strengthening the antioxidant defense system, thereby reducing oxidative stress and accelerating mucosal wound healing.

The findings also showed that star fruit ethanol extract significantly reduced MDA levels and increased fibroblast proliferation in mucosal wounds. Group II (20% extract) had an average MDA level of 4.70 ± 2.99, markedly lower than group I (10% extract, 12.4 ± 1.71) and the positive control group treated with triamcinolone acetonide 0.1% (25.1 ± 2.52). The post-hoc test confirmed these differences were significant ($p = 0.002$).

Moreover, fibroblast counts in group II (234.0 ± 11.8) were higher compared to group I (194.4 ± 25.4) and the positive control (220.0 ± 4.09), with a post-hoc test yielding $p = 0.004$. These findings suggest a dose-response relationship, where increasing extract concentration from 10% to 20% enhances antioxidant effects and stimulates fibroblast proliferation, leading to improved tissue regeneration. Bioactive compounds such as flavonoids in star fruit appear to reduce lipid peroxidation (as indicated by decreased MDA levels) while also supporting fibroblast growth, thereby expediting the wound healing process. The clear differences between treatment groups I and II strengthen the hypothesis that the therapeutic potential of star fruit extract is dose-dependent, with 20% concentration proving more effective in promoting tissue recovery (Dong et al., 2021).

Previous histological studies also reported that star fruit extract has antioxidant properties capable of preventing oxidative damage to hepatocytes and maintaining cellular integrity in diabetic rats (Li et al., 2021). Phenolic and flavonoid compounds from star fruit have been shown to possess both antioxidant and antibacterial activity (Iwansyah et al., 2021). Herbal plants, especially those rich in flavonoids, are known to accelerate wound healing by scavenging free radicals, enhancing tissue contraction, and promoting angiogenesis and fibroblast proliferation (Hua et al., 2022). Increased blood flow in injured tissue elevates endothelial cells, macrophages, and fibroblasts, which are critical in collagen synthesis (Mahran & Aborehab, 2021). Collagen formation is closely linked to fibroblast proliferation and differentiation during wound healing (Unnikrishnan et al., 2021). The findings of this study confirm these mechanisms, showing significantly higher fibroblast proliferation in group II (234.0 ± 11.8) compared to group I (194.4 ± 25.4). Statistical analysis ($p = 0.002$) reinforces the conclusion that 20% ethanol extract of star fruit is more effective in stimulating fibroblast growth than 10% concentration. This supports the notion that the therapeutic benefits of belimbing wuluh in wound healing are strongly associated with its antioxidant capacity and fibroblast-stimulating properties.

CONCLUSION

Based on the results of this study, ethanol gel extract of starfruit (*Averrhoa bilimbi Linn.)* was found to be effective in enhancing antioxidant activity in traumatic wounds in rats. Flavonoids, as the main active component, played a crucial role in reducing oxidative stress and accelerating the wound healing process. The findings also demonstrated that ethanol extract of belimbing wuluh significantly increased fibroblast proliferation in mucosal wounds, with the 20% concentration showing greater efficacy compared to the 10% concentration. These results highlight the potential of starfruit extract as a natural-based therapy for wound management, either as an alternative or adjunct to conventional treatment.

Nevertheless, this study has certain limitations, including the relatively short experimental duration of five days, the use of only one animal model (Wistar rats), which may not fully reflect human clinical conditions, and the absence of a comprehensive dose-response analysis to determine the optimal concentration. Therefore, further investigations are recommended with extended experimental periods, the use of diverse animal models or clinical trials in humans, and detailed exploration of dose-response relationships. Such studies will provide stronger evidence on the effectiveness of starfruit extract in improving wound healing and reducing oxidative stress, thereby broadening its potential application in clinical practice.

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