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PHARMACOLOGICAL INVESTIGATION OF THE ORAL WOUND HEALING ACTIVITY OF *Stachytarpheta jamaicensis* ROOT EXTRACT GEL IN WISTAR RATS

Investigasi Farmakologis Aktivitas Penyembuhan Luka Mulut Gel Ekstrak Akar *Stachytarpheta jamaicensis* pada Tikus Wistar

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ABSTRACT

The Stachytarpheta jamaicensis (L) Vahl root contains bioactive compounds like saponins, alkaloids, flavonoids, tannins, phenols, and terpenoids, which have antibacterial and anti-inflammatory properties. This study investigates the wound healing effects of *Stachytarpheta jamaicensis* (L) Vahl root extract gel in oral mucosa. The experiment involved 28 male Wistar rats, divided into four groups: a positive control treated with povidone iodine 10%, a negative control treated with gel base, and two experimental groups treated with 6% and 10% S. jamaicensis root extract gels. The gel was applied twice daily, and wound healing was assessed by epithelial thickness, inflammation cell and hydroxyproline content. Both concentrations of *S. jamaicensis* root extract gel significantly enhanced wound healing, as shown by increased epithelial thickness, inflammation cell and hydroxyproline content levels compared to the negative control. These findings suggest that *S. jamaicensis* root extract gel effectively promotes wound healing in the excision wound model.

Keywords: *Epithelialization. Hydroxyproline. Inflammation Cells. Stachytarpheta jamaicensis. Wound healing*

ABSTRAK

Akar *Stachytarpheta jamaicensis (L) Vahl* mengandung senyawa aktif seperti saponin, alkaloid, flavonoid, tanin, fenol, dan terpenoid, yang berkontribusi secara signifikan dalam penyembuhan luka melalui efek antibakteri dan antiinflamasi. Penelitian ini bertujuan untuk mengevaluasi pengaruh gel ekstrak akar *S. jamaicensis* dengan konsentrasi 6% dan 10% terhadap ketebalan epitel dan kandungan hidroksiprolin selama proses penyembuhan luka pada mukosa mulut. Penelitian ini menggunakan desain eksperimental murni dengan kelompok kontrol posttest-only. Sebanyak 28 ekor tikus jantan galur Wistar dibagi menjadi 4 kelompok,

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yaitu satu kelompok kontrol positif yang diberi povidone iodine 10%, satu kelompok kontrol negatif yang diberi basis gel, dan dua kelompok eksperimen yang diberi gel yang mengandung ekstrak akar S. jamaicensis 6% dan 10%. Perawatan diterapkan dua kali sehari. Efek penyembuhan luka dievaluasi berdasarkan ketebalan epitel dan kadar hidroksiprolin pada model luka eksisi. Konsentrasi 6% dan 10% gel ekstrak akar *S. jamaicensis* secara signifikan meningkatkan penyembuhan luka, yang dibuktikan dengan peningkatan ketebalan epitel dan kadar hidroksiprolin dibandingkan dengan kelompok kontrol negatif. Gel ekstrak akar S. jamaicensis pada konsentrasi 6% dan 10% efektif.

Kata kunci: *Epitelisasi. Hidroksiprolin. Sel Inflamasi. Stachytarpheta jamaicensis. Penyembuhan luka*

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INTRODUCTION

A wound occurs when a part of the body's tissue is damaged or lost due to various causes such as sharp injuries, impacts, temperature changes, chemicals, electric shock, or animal bites [1]. In dentistry, one common type of wound is a traumatic ulcer, which results from heat, friction, or contact with sharp objects [2]. Traumatic ulcers are widespread, with a prevalence of 93.3% in Indonesia [3]. Although these ulcers usually resolve within two weeks once the cause is removed, medication can help prevent infection during the healing process [4].

The wound healing process involves three stages: inflammation, proliferation, and maturation [5]. In the early stage, inflammation occurs as the body’s response to injury, leading to swelling, redness, and pain as white blood cells work to clear the wound of germs and dead cells. In the proliferation stage, the body begins to form new tissue, including the creation of new blood vessels, collagen production, and the covering of the wound surface with new epithelial cells. The epithelium is the outermost layer of tissue, including mucosal tissue, which protects the underlying tissues from mechanical, chemical, and thermal trauma. Epithelialization is a critical step in healing oral mucosal wounds, such as canker sores, where it helps restore tissue integrity. The formation of epithelial tissue in superficial wounds typically takes about seven days, depending on the wound size. The faster the epithelialization process, the quicker the wound heals [6,7]. In the maturation stage, the newly formed tissue matures, and the wound strength increases as more collagen is produced [8]. The healing process is not considered complete until the damaged surface is securely bonded through collagen formation, which significantly increases by day 7 after wounding [9,10].

Collagen is an essential protein that strengthens the new tissue formed during wound healing [11]. Collagen fibers are composed of three main amino acids: proline, glycine, and hydroxyproline. Hydroxyproline makes up about 13.4% of the total amino acids in collagen and has a unique structure, which makes it commonly used as a quantitative marker for collagen deposition in wound healing [12]. High levels of hydroxyproline indicate increased collagen synthesis, suggesting faster wound healing. In contrast, low levels of hydroxyproline indicate a slower healing process [13]. The wound healing process can generally be aided by povidone iodine, which has antiseptic properties; however, it may cause irritation at high concentrations. Therefore, natural medicinal preparations, such as *Stachytarpheta jamaicensis* (L) Vahl, which contains various active compounds, can serve as a safer and more economical alternative for wound management [14,15].

The potential of *Stachytarpheta jamaicensis* root extract (SJRE) is highlighted in the study by Utami et al. (2022), which demonstrates that SJRE contains compounds with anti-inflammatory and antibacterial properties, making it beneficial for wound healing [16]. However, there has been no research on the effects of *S. jamaicensis* root extract gel on epithelialization and oral wound healing. This study aims to assess the impact of *S. jamaicensis* root extract gel on epithelialization and hydroxyproline content in excision wounds on the buccal mucosa of Wistar rats.

MATERIALS AND METHODS

Experimental Animals

This research has been reviewed and approved by the Health Research Ethics Commission of FKG ULM, with Ethics Feasibility Letter No. 154/KEPKG-FKGULM/EC/XII/2023. The study employs a pure experimental method using a post-test only design with a control group. A total of 28 male Wistar rats were selected through simple random sampling, based on specific inclusion and exclusion criteria. The rats were acclimated to the cage environment and research site for 7 days prior to the experiment. The sample was divided into four groups: Group 1 (treatment group with 6% concentration SJRE), Group 2 (treatment with 10% concentration SJRE), Group 3 (positive control group with povidone iodine preparation), and Group 4 (negative control group with gel without SJRE content). Each group consisted of 7 healthy male Wistar rats, each weighing between 200 and 250 grams. Feeding and drinking were provided ad libitum.

Gel Extract Preparation

The roots of *S. jamaicensis* were collected from Sungai Abit Village, Cempaka District, Banjarbaru City, South Kalimantan. The fresh roots, approximately 10 cm in length, were carefully washed, weighed (3 kg), and then dried. They were cut into smaller pieces and placed in an oven at 80°C for 24 hours. After drying, the roots were pulverized using a blender. Maceration was performed by placing 600 g of the powdered *S. jamaicensis* roots into an extractor, then adding 6000 ml of 96% ethanol (at a 1:10 ratio), and stirring for 24 hours until a homogeneous mixture was achieved. This process was intended to ensure the active compounds in the roots dissolved into the ethanol. The resulting extract was then filtered, and the residue was re-extracted in the same manner five times. The extract was filtered again and concentrated using a rotary vacuum evaporator at 59-60°C until a concentrated extract was obtained. Subsequently, the extract was heated in a water bath until the solvent was fully evaporated, as indicated by the absence of steam droplets, resulting in a thick extract. The ethanol content of the extract was tested by adding potassium chromate (K_2CrO_4) and concentrated sulfuric acid (H_2SO_4), and observing any resulting color change [17].

The gel base is prepared according to the following procedure: 5 g of Na-CMC, 10 g of glycerin, and 5 g of propylene glycol are placed into a glass beaker and stirred with a stirring rod until homogeneous [18,19]. This mixture is then heated on a hot plate at 50°C. Once the components are well mixed, distilled water (aquadest) is added until the total volume reaches 100 ml, and the mixture is stirred until fully blended and homogeneous.

For the preparation of gel formulations with varying concentrations of *S. jamaicensis* root extract, the previously prepared gel base is combined with each extract concentration and stirred until homogeneous. The root extract concentrations used in this study were 6% and 10%. The formula is observed in the Table 1.

Table 1. Composition of *S. jamaicensis* Root Extract Gel Variations

No	Ingredient	Function	Composition (%w/w)		
			F1 (6%)	F2 (10%)	F3 (Gel base)
1	S. *jamaecensis root extract*	Active agent	1.8%	3%	-
2	Na-CMC	Gelling agent	1.67%	1.67%	1.67%
3	Propylene glycol	Humectant	3.34%	3.34%	3.34%
4	Glycerin	Emollient	1.67%	1.67%	1.67%
5	Aquadest	Solvent	33.34 ml	33.34 ml	33.34 ml

Experimental Animal Treatment

In this study, Wistar rats were selected based on their healthy condition, with no body weight fluctuations exceeding 10% and displaying normal behavior. The experimental animals, which had been acclimatized for 7 days, were then assigned a group code. The rats were anesthetized by

intramuscular injection of 1-2 mg/kg xylazine hydrochloride and 10 mg/kg ketamine hydrochloride. An excision was made using a punch biopsy tool with a cross-sectional area of approximately 5 mm² on the buccal mucosa of the right side of each rat. Any excess blood was removed using cotton and water [20,21]. The application of *S. jamaicensis* root extract gel was performed by administering 0.1 ml to the experimental animals twice daily, starting from the day of wounding and continuing until the 7th day for each group.

Histopathological Analysis

Wound tissue samples from all groups, were harvested on day 7, after wound injury, for histological analysis. Samples were fixed in 4% paraformaldehyde solution (pH 7.4) for 24 h, dehydrated, cleared and embedded in paraffin. Sections (5 µm-thick) were mounted on adhesive glass slides and stained with hematoxylin-eosin (HE), using standard procedures. The stained tissue sections were observed and the images captured under a light microscope (Olympus BX3-CBH, Massachusetts, USA.) [22].

Homogenate Preparation

The mucosal tissue samples were tested for hydroxyproline content. A high concentration of hydroxyproline indicates elevated collagen production. Collagen plays a crucial role in stimulating platelet activation, aggregation, and the production of chemotactic factors to initiate the healing process [13]. The tissue was first dried for 12 hours at 60°C in an oven. After drying, the tissue was immersed in a 6N HCl solution and heated to 130°C to break down the protein and release hydroxyproline. Following hydrolysis, the solution was neutralized to pH 7 using NaOH and then oxidized with Chloramine-T for 20 minutes. Staining was performed using Ehrlich's reagent, and the samples were incubated at 60°C.

Observation

Histopathological observations of epithelial thickness were made by drawing a straight line from the stratum basale to the stratum corneum using a light microscope with a 40x objective lens, achieving a magnification of 400x. For cell counts were observed and the images captured under a light microscope (Olympus BX3-CBH) [22]. The hydroxyproline content was measured by assessing its absorbance at a wavelength of 557 nm using a UV-Vis spectrophotometer. The concentration of hydroxyproline was determined by comparing the absorbance of the samples to a standard curve.

Statistical Analysis

The statistical analysis for hydroxyproline content and inflammation cells data was performed using the one-way analysis of variance (ANOVA) method, followed by the Tukey's post hoc test. Then, the analysis for the epithelization was performed using Mann Whitney method followed by the Bonferroni's post hoc test. Data processing and analysis were performed using the SPSS software (Manufactured by IBM Corp., N.Y., USA), and the results of the One-Way ANOVA analysis showed a p-value of < 0.05, indicating that the data are statistically significant.

RESULTS

Epithelial Thickness

The research data were obtained by observing histopathological preparations at a magnification of 400x, divided into three fields of view, which produced an image of pinkish-purple epithelial tissue. The results of the histopathological observations are shown in Figure 1.

Histopathological analysis revealed that the epithelial thickness, measured from the stratum basalis to the stratum corneum, was greatest in the 6% group, which exhibited denser tissue than the other groups. The epithelial tissue appeared pinkish-purple in color, with blue, round cells scattered throughout the tissue.

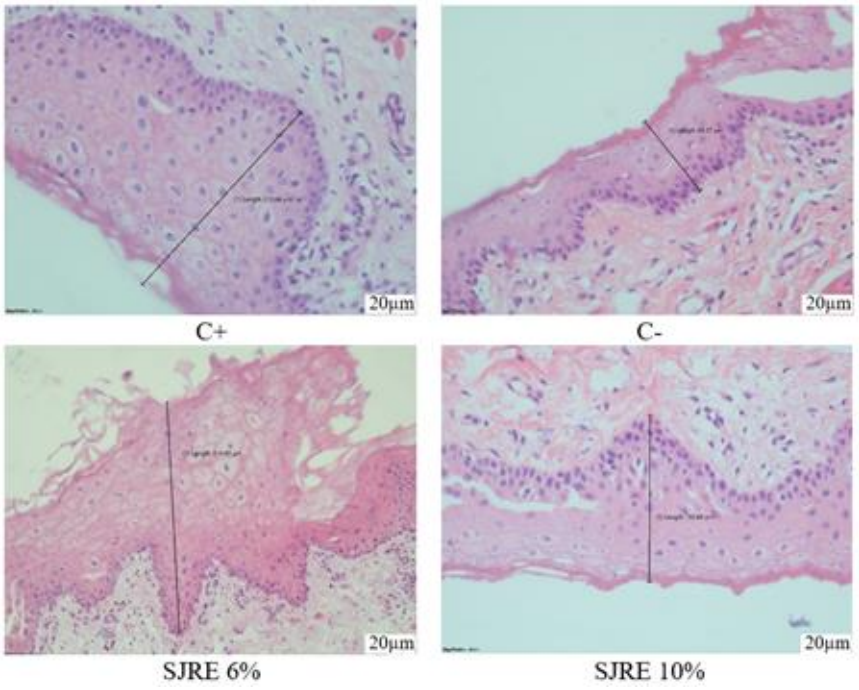

Figure 1. Histological images of hematoxylin and eosin stained crosssectioned tissue samples of buccal wound of rats obtained day 7 post-injuries, treated with gel base, 6% SJRE gel and 10% SJRE gel. (magnification ×40). The thickness of the epithelium, measured from the stratum basale to the stratum corneum, showed the highest value in the 6% SJRE gel group, with a denser tissue density compared to the other groups.

This figure shows the average epithelial thickness in the excision wounds of the buccal mucosa in Wistar rats (Rattus norvegicus) from the four groups on day 7. The highest mean epithelial thickness was found in the group treated with 6% *S. jamaicensis* root extract gel. The group with the next highest mean value was the positive control group, which was treated with povidone iodine, slightly lower than the 6% group. This was followed by the 10% group, which had a slightly higher value than the negative control group, which was treated with only the gel base, without any extract.

The results of the Post Hoc Bonferroni test indicated significant differences ($p<0.05$) between the groups. Notably, significant differences were observed between the 6% treatment group and the negative control group ($p=0.380$), as well as between the positive control group and the negative control group ($p=0.381$).

Hydroxyproline Contents

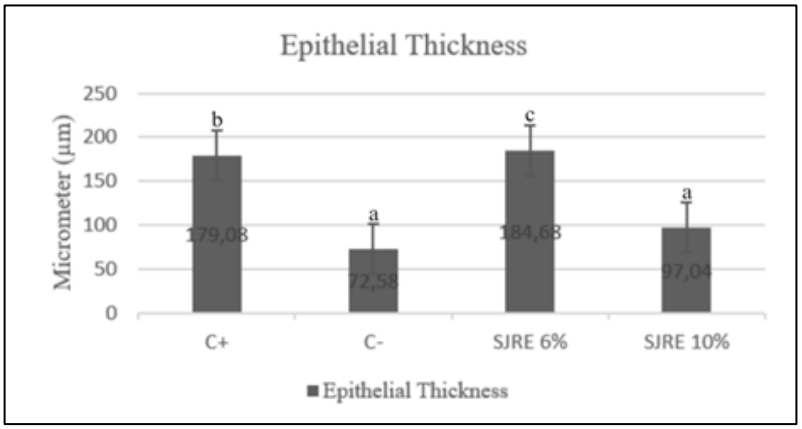

Figure 2. Average epithelial thickness of buccal mucosa excision wounds in Wistar rats (*Rattus norvegicus*) on day 7

**abcd = Different superscripts inidicate statistically significant differences across treatments ($p<0.05$)*

Figure 2 shows that the SJRE 10% group exhibits the highest hydroxyproline concentration (0.816 mg/mL), followed by the SJRE 6% group (0.624 mg/mL), the positive control group (povidone iodine, 0.5 mg/mL), and the negative control group (gel base), which has the lowest hydroxyproline concentration (0.284 mg/mL). High hydroxyproline content reflects increased collagen synthesis and accelerated wound healing, while low levels may indicate potential delays in the healing process.

The results of the Mann-Whitney test show a significant difference between the negative control group and the groups treated with *S. jamaicensis* root extract gel (SJRE 6% and 10%). The positive control group (povidone iodine) also shows a significant difference compared to all groups treated with *S. jamaicensis* root extract gel (SJRE 6% and 10%). Significant differences were also observed between the SJRE 6% group and all other treatment groups, as well as between the SJRE 10% group and all other treatment groups.

Based on the data provided, a statistical analysis was conducted to compare the effects of the Negative Control, Positive Control, 6%, and 10% treatments on three variables: Fibroblast, Macrophage, and Lymphocyte counts. The results for fibroblast counts showed a significant reduction in the 6% and 10% treatment groups, with values of 54.5 and 51.57, respectively, compared to the higher counts in the Negative Control (130) and Positive Control (121) groups. This difference was statistically significant, as indicated by $p = 0.00$. This suggests that the treatments significantly reduce fibroblast activity, possibly affecting tissue regeneration or wound healing.

In contrast, the macrophage counts did not show a significant difference between the groups. The p-value for macrophages was 0.076, which is greater than 0.05, indicating no statistically significant difference across the groups. This suggests that the treatments did not have a strong effect on macrophage levels, implying that these immune cells were not notably impacted by the treatments in this study. Similarly, the lymphocyte counts also showed no significant differences across the groups, with $p= 0.23$. This indicates that in the day 7, the treatments did not significantly alter lymphocyte activity.

DISCUSSION

The results of this study demonstrate that the application of *S. jamaicensis* root extract gel at concentrations of 6% and 10% increases epithelial thickness compared to the negative control on day 7. Both concentrations of *S. jamaicensis* root extract gel also significantly increased hydroxyproline content compared to the negative control and positive control (Figure 2). This effect is attributed to the active compounds present in the *S. jamaicensis* root extract, which can accelerate wound healing. In contrast, the negative control did not receive any treatment to stimulate faster healing. The active compounds in *S. jamaicensis* root include saponins (31.602%), alkaloids (17.64%), flavonoids (1.875%), terpenoids (1.4%), and tannins (0.052%) [24]. These compounds not only function as antioxidants, helping to reduce inflammation, but also play a direct role in the proliferation process, leading to increased epithelial thickness and enhanced collagen production, which correlates with increased hydroxyproline levels (Figure 3).

During the initial stage of wound healing, in the inflammatory phase, the number of neutrophils increases due to the presence of pathogens or injury. These neutrophils serve to prevent infection. Eventually, they undergo apoptosis, and their numbers decrease as they are cleared by phagocytosis performed by macrophages. The activity of macrophages can be enhanced by saponins and flavonoids, which are secondary compounds present in high concentrations in *S. jamaicensis* root extract. Flavonoids act as immunomodulators by increasing the production of interleukin (IL-2), which, in turn, stimulates lymphocyte proliferation and T cell differentiation into T helper 1 (TH1) cells. These lymphocytes then activate CD4+ cells, which further stimulate TH1 cells. T helper 1 (TH1) cells influence the production of Specific Macrophage Activating Factor (SMAF), including interferon gamma (IFN-γ), which activates macrophages [25,26].

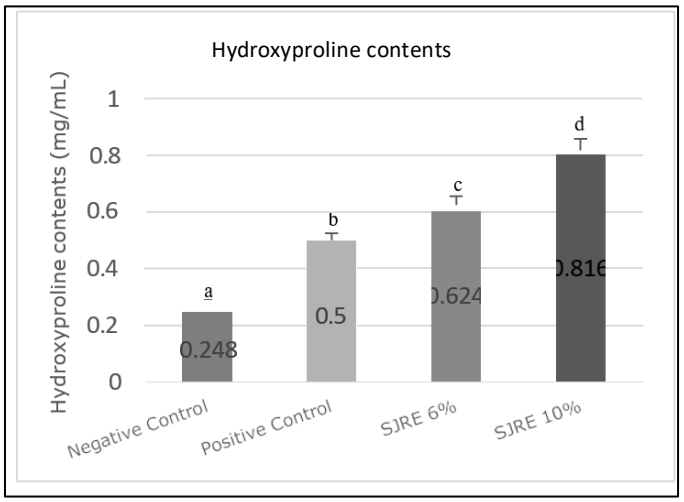

Figure 3. *Average Hydroxyproline* Contents level of buccalmucosa excision wounds in Wistar rats (*Rattus norvegicus*) on day 7
*abcd = Different superscripts inidicate statistically significant differences across treatments ($p<0.05$)

The inflammation cells activity will be facilitated by saponins, which infiltrate inflammatory cells and promote the accumulation of macrophages in blood vessels. The number of macrophages will continue to rise as they carry out their role in the wound healing process. Any excessive accumulation of macrophages will be regulated by the anti-inflammatory cytokine IL-10. IL-10 is an anti-inflammatory cytokine produced by macrophages, B cells, and T cells. It reduces the sensitivity of macrophages and dendritic cells in assisting T-cell activation by suppressing MHC-II expression on the surface of macrophages. This suppression leads to the inhibition of both non-specific and specific inflammatory reactions mediated by T cells. This process is further supported by the secondary compounds luvangetin and xanthyletin, which are present in *S. jamaicensis* root extract [16,27].

Based on the research conducted by Utami et al. (2022), it was found that *S. jamaicensis* root extract contains secondary metabolites, luvangetin and xanthyletin, which belong to the coumarin group. These compounds exhibit antifungal, antiulcer, and antibacterial properties. *S. jamaicensis* root extract has been shown to inhibit the growth of bacteria such as *Aggregatibacter actinomycetemcomitans*, *Enterococcus faecalis*, and *Actinomyces* spp., which are commonly found in the oral cavity [16,28]. The antiulcer properties associated with wound healing, attributed to the activity of luvangetin and xanthyletin, can aid in increasing the secretion of the anti-inflammatory cytokine IL-10 during the wound healing process. This occurs through the inhibition of proinflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-12. The increased secretion of IL-10 prevents prolonged inflammation, thereby reducing severe tissue damage. As a result, the processes of epithelialization and collagen synthesis in the subsequent phases can proceed optimally [29].

Saponins, which are secondary metabolites in *S. jamaicensis* root extract, play a crucial role in the angiogenesis process by enhancing the activity of vascular endothelial growth factor (VEGF). VEGF stimulates the formation of new cells, including endothelial cells, smooth muscle cells, and fibroblasts [30]. The fibroblasts, in turn, secrete various matrix metalloproteinases (MMPs) that replace extracellular matrix (ECM) components such as collagen, proteoglycans, laminin, and others. This ECM complex supports fibroblast migration and activity, facilitating tissue repair. Additionally, fibroblasts synthesize type III collagen and fibronectin, which promote fibrin clot formation and aid in the re-epithelialization process. Type III collagen peaks on day seven and is gradually replaced by type I collagen during the remodeling phase [11,26,30].

However, the results of hidroxyproline content and epithel thickness is not in line with inflammation cells expression. There were low level of fibroblasts, macrophages

and lymphocytes expression in day 7 for all groups in this study (Table 2). It was related to the initial stage of inflammation in oral wound healing showed fewer resident cytokines, a decrease in blood vessels, and rapid fibroblast formation at the wound site [31]. There is faster wound healing process in oral mucose due to some factors such as bulge cells, saliva and genomic patterns [31, 32]. Priprem et al. (2018) performed a wound procedure using a 5 mm² punch biopsy, which showed good wound closure by the fifth day [33]. Therefore, the expression of fibroblast cells was observed to decrease by the seventh day, as the wound had fully closed, as indicated by high hydroxyproline levels and good epithelial thickness.

Table 2. The average number of fibroblasts, macrophages, and lymphocytes

Variable	Negative Control (n=7)	Positive Control (n=7)	6% (n=7)	10% (n=7)	P
Fibroblast	130 ± 25,22	121 ± 35.78	54.5 ± 23.06	51.57 ± 25.10	0.00*
Macrophage	34 ± 11.6	20 ± 5.7	28 ± 27	9.8 ± 5.1	0.076*
Lymphocyte	110.00 ± 60.28	85 ± 20.03	57.00 ± 45.92	75.00 ± 33.03	0.23

***** Data are presented as Mean ± SD. Data differences (p) are declared significant if $p < 0.05$.

Furthermore, the alkaloids in this extract act as antioxidants by inhibiting the enzyme NADPH oxidase, which reduces the production of reactive oxygen species (ROS)[34]. High levels of ROS can induce oxidative stress, hinder wound healing, and worsen inflammatory reactions. By reducing ROS, alkaloids help accelerate wound healing by shortening the inflammatory response and promoting fibroblast proliferation for collagen production. Alkaloids also contribute to strengthening collagen fibrils, enhancing the strength of newly formed tissue during the re-epithelialization process [11,35].

The flavonoids in this extract also function as antioxidants by neutralizing free radicals directly, providing hydrogen ions, and enhancing the activity of antioxidant genes in the body through the activation of nuclear erythroid 2-related factor 2 (Nrf2). Flavonoids increase the production of TGF-β, which stimulates fibroblast activation and promotes collagen production. This process helps accelerate wound healing by increasing the number of macrophages involved in collagen production [35]. By boosting macrophage participation in collagen synthesis, flavonoids contribute to the overall acceleration of the re-epithelialization process [16,27].

In this study, the hydroxyproline content in wounds treated with 10% povidone iodine was significantly lower compared to the groups treated with *S. jamaicensis* root extract gel. This is because 10% povidone iodine and *S. jamaicensis* root extract have different mechanisms of action in wound healing. Povidone iodine 10% primarily acts as a wound healing agent through its antibacterial properties and does not directly enhance hydroxyproline levels [14]. Additionally, 10% povidone iodine is known to inhibit fibroblast proliferation, potentially interfering with the collagen formation process mediated by hydroxyproline, which may slow down the wound healing process [36]. The differing mechanisms of action between povidone iodine 10% and *S. jamaicensis* root extract lead to significant differences in hydroxyproline content between the two treatments. As a result, the hydroxyproline content in wounds treated with povidone iodine 10% in this study was notably lower compared to those treated with *S. jamaicensis* root extract gel.

The increase in epithelialization thickness in the 10% group was not greater than in the 6% group, likely due to the high concentration of the mixed compound, which could potentially affect the healing process. This occurs because, under certain conditions, herbal remedies at higher doses or concentrations may become less effective. This phenomenon arises from the fact that the active compounds involved are not singular; rather, they consist of numerous compounds that interact with each other during the process [30]. However, with a higher dosage, the number of active compounds

increases, which may lead to interactions that reduce overall effectiveness.

The study on *S. jamaicensis* root extract gel has demonstrated its potential to accelerate the wound healing process, attributed to the synergistic effects of its various active compounds. These compounds significantly enhance macrophage activity, fibroblast proliferation, and collagen synthesis, while also playing a critical role in the re-epithelialization process. The findings suggest that *S. jamaicensis* root extract gel could be a promising natural alternative for wound management.

This research is limited to excisional buccal mucosal wounds in normal rats without any underlying disorders or complications. Therefore, the results may not fully reflect the effects of *S. jamaicensis* root extract gel on wounds in models with comorbidities or chronic conditions. To build on these findings, more in-depth research is needed to explore the toxicity profile of *S. jamaicensis* root extract, as safety is a crucial consideration for its widespread use in clinical applications. Additionally, future studies should focus on identifying and assessing specific biomarkers involved in wound healing, such as growth factors and cytokines, to gain a deeper understanding of how the active compounds in *S. jamaicensis* contribute to the healing process at the molecular level. Moreover, investigating the potential cytotoxicity and genotoxicity of the extract will be important to ensure that it does not cause adverse effects, especially when used over long periods.

CONCLUSION

Overall, *S. jamaicensis* root extract gel has been shown to accelerate the wound healing process due to the synergistic effects of various active compounds. These compounds not only enhance macrophage activity, fibroblast proliferation, and collagen synthesis but also play a crucial role in the re-epithelialization process.

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