Effectiveness of Licorice Extract (*Glycyrrhiza glabra L.*) on Traumatic Ulcer with Parameter Study: Macrophage, Neutrophil, and Lymphocyte

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ABSTRACT

***Background**: Traumatic oral ulcers involve epithelial loss, pain, and erythematous halos, heal through four wound healing stages. This study evaluated licorice root (Glycyrrhiza glabra L.), recognized for its anti-inflammatory and immunomodulatory properties, for its effect on macrophage, neutrophil, and lymphocyte counts during ulcer healing.*
***Methods**: A post-test-only design included five groups of six mice each: three received 5%, 10% and 15% licorice extract, and two served as controls (Aloclair as positive, Aquadest as negative). Treatments were administered twice daily for three days using a nanomouth spray after ulcer were induced on the labial mucosa with heated burnisher. Following euthanasia, labial tissues were fixed, processed, and stained with Haematoxylin-Eosin for histological analysis at 400x magnification.*
***Result**: Phytochemical analysis showed high flavonoid (44.669) and saponin (38.802) levels in the licorice extract. Statistical analysis revealed significant differences between groups ($p < 0.05$) in macrophage, neutrophil, and lymphocyte counts. The 10% extract group had the highest mean counts per field for macrophages (35.2 ± 2.1), neutrophils (18.7 ± 1.9), and lymphocytes (22.9 ± 2.3), indicating optimal anti-inflammatory and immunomodulatory effects at this concentration.*
***Conclusion:** Licorice extract promotes healing of traumatic oral ulcers. The 10% extract was most effective, accelerating healing and regulating inflammatory cell activity more than other concentrations or controls*

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INTRODUCTION

Ulcer is defined as the loss of epithelial integrity extending to the basement membrane and involving the lamina propria.[1] Traumatic oral ulcers are a common condition characterized by the loss of the entire epithelium, often presenting as painful, well-circumscribed lesions with an erythematous halo.[2–4] These ulcers can be caused by various types of trauma, including mechanical and chemical injuries.[3] Traumatic ulcers typically present as single, painful lesions with a yellow-white fibrin clot covering the epithelial defect.[5]

Traumatic ulcer healing involves four phases: hemostasis, inflammation, proliferation, and remodeling, which restore tissue integrity.[6] During the inflammatory phase, neutrophils and macrophages infiltrate the wound. Neutrophils remove foreign materials and bacteria through phagocytosis, while macrophages continue this process and release growth factors.[7] Macrophages are classified as pro-inflammatory, active in the early inflammatory phase, and anti-inflammatory or pro-angiogenic, active later.[8,9] Lymphocytes, including T cells and B cells, are recruited to the wound site during the inflammatory phase. They interact with other immune cells such as neutrophils and macrophages to regulate the immune response.[10] Regulatory T cells (Tregs) and regulatory B cells (Bregs) modulate the immune response to limit inflammation and support tissue repair.[11]

The effectiveness of topical corticosteroids in managing traumatic ulcers is mixed. Corticosteroids are recognized for their anti-inflammatory properties, which can reduce inflammation in traumatic ulcers and may accelerate healing.[2] However, some studies indicate that topical corticosteroids can also delay healing. For example, an in vivo study with Wistar rats found that the corticosteroid group had a longer healing time than the control group. Thus, while corticosteroids reduce inflammation, their effect on healing remains uncertain.[12] Natural ingredients like Licorice extract have shown promise in accelerating the healing process of traumatic ulcers.

Licorice (*Glycyrrhiza glabra L*) is a herbal compound known to exhibit anti-inflammatory, antimicrobial, and antioxidant properties.[13] Licorice contains several bioactive compounds, including glycyrrhetinic acid, glycyrrhizin liquiritigenin, which are primarily responsible for its therapeutic benefits.[14] Glycyrrhizin, the principal bioactive constituent of licorice root, belongs to the class of triterpenoid saponins and is recognized for its intense sweetness, estimated to be approximately 50 times greater than that of sucrose.[15] Glycyrrhizin is hydrolyzed into glycyrrhetinic acid, which is primarily responsible for its anti-inflammatory properties.[16,17] Despite its therapeutic potential, scientific evidence regarding the efficacy of licorice root in promoting ulcer healing remains limited. Therefore, further investigation is warranted to explore its role as a natural alternative in the management of traumatic ulcers.

RESEARCH METHOD

This study employed a post-test-only group design, in which measurements were taken after treatment. Subjects were divided into five groups, comprising three treatment groups and two control groups. The treatment groups included: Group 1, which received 5% licorice root extract; Group 2, which received 10% licorice root extract; and Group 3, which received 15% licorice root extract. The positive control group was treated with Aloclair, while the negative control group received distilled water (Aquadest). Each group consisted of six subjects, for a total of 30 subjects in this study. Subject selection was conducted in accordance with predefined inclusion and exclusion criteria to ensure the appropriateness of the sample and research validity.

The research material was licorice root (*Glycyrrhiza glabra L.*), sourced from the Functional Implementation Unit (UPF) of RSUP Dr. Sardjito Tawangmangu, Karanganyar Regency, Central Java. Before extraction, the test material underwent phytochemical screening to confirm the presence of active compounds. The phytochemical screening in this study was conducted using the organoleptic method. The analysis specifically identified flavonoids and saponins as the primary bioactive constituents responsible for licorice extract's pharmacological activity.

The extraction of licorice root (*Glycyrrhiza glabra L.*) began with the removal of surface impurities. Next, the roots were sun-dried in the morning until fully desiccated and then ground into a fine powder. About 1 kg of the powder was macerated in 10 liters of 96% ethanol with continuous stirring for 4 hours. The mixture was then left to stand for 24 hours to complete maceration. It was filtered until a clear, colorless filtrate formed. This filtrate was concentrated using a rotary vacuum evaporator at 50°C and 70 rpm until a viscous extract resulted. The extract was refrigerated until needed for experimentation.

Ulceration was induced in experimental animals by first applying 10% benzocaine to the labial mucosa of rats to minimize pain. After ensuring adequate anesthesia, a heated round burnisher (2 mm in diameter and red-hot) was pressed on the labial mucosa for one second to cause a localized thermal injury. Ulcerative lesions appeared and became visible about two days after the procedure.

The extract was administered to all experimental groups twice daily—morning and evening—using a nano-mist spray for three days. After treatment, tissue sampling was performed. Each group of animals was euthanized in accordance with ethical guidelines. Labial mucosal tissue was excised from each group and sectioned into specimens approximately 5 × 5 mm and 2–3 mm thick using a scalpel and scissors. The samples were then fixed in formalin, embedded in paraffin, and sectioned for histological examination.

Histopathological preparation was carried out for tissue analysis. Harvested tissue was fixed in 10% formalin for 24 hours to preserve cellular architecture. After fixation, the tissue was dehydrated in graded ethanol, cleared with xylene, and embedded in paraffin. Paraffin blocks were sectioned at 5 micrometers using a microtome and mounted on glass slides. Specimens were stained with Hematoxylin and Eosin (H&E) to visualize histological structures, including the quantity and morphology of inflammatory cells such as macrophages, neutrophils, and lymphocytes. Histological evaluation was performed under a light microscope by an observer blinded to the treatment groups to minimize assessment bias. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Dentistry, Universitas Islam Sultan Agung, Semarang (701/B.1-KEPK/SA-FKG/III/2025).

RESULTS

A phytochemical analysis of licorice (*Glycyrrhiza glabra L.*) was conducted using the IUBIO spectrophotometric method, which identified bioactive compounds, specifically flavonoids and saponins. Flavonoid concentration was 44.669 mg/g, and saponin concentration was 38.802 mg/g.

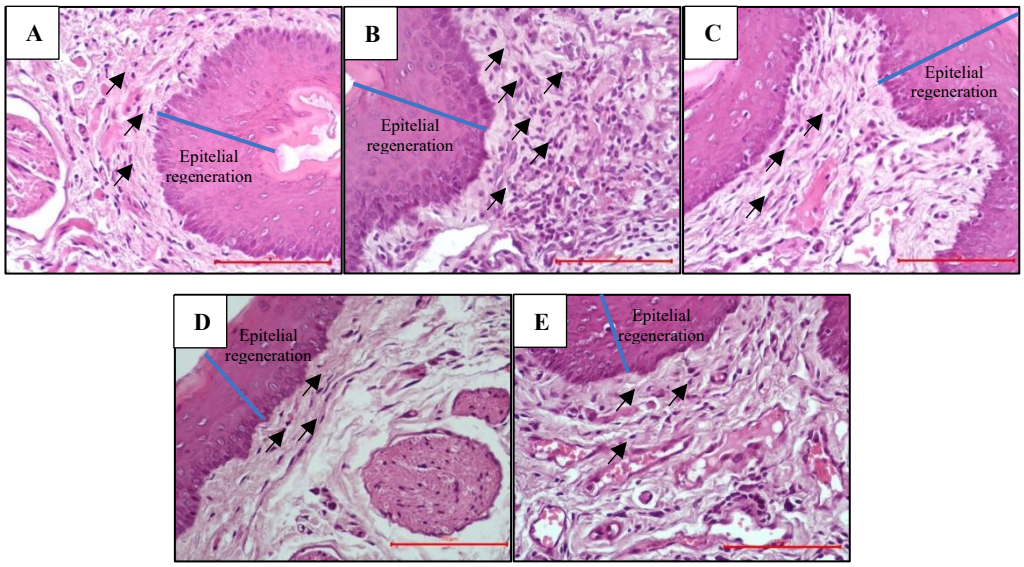

Figure 1. Histological images of thickness of the ulcer epithelium, 5% licorice extract (A), 10% licorice extract (B), 15% licorice extract (C), positive control (D), and negative control (E). The blue line indicates the thickness of the epithelium from the stratum basale to the stratum corneum and the arrows indicate fibroblast activity at 400x magnification.

The histological observations shown in Figure 1 illustrate differences in tissue-healing responses among the experimental groups. The 10% licorice extract group (B) exhibited the most organized epithelial regeneration, reduced inflammatory cell infiltration, and increased fibroblast activity, indicating an advanced stage of wound healing. In contrast, the 5% (A) and 15% (C) extract groups showed less optimal healing, characterized by moderate inflammatory cell presence and incomplete epithelial repair. The positive control group (D) demonstrated healing consistent with a mild therapeutic response, whereas the negative control group (E) showed persistent inflammation and tissue disruption.

Table 1. Results of normality, homogeneity, and statistical comparison of macrophage cells

Group	Mean	Shapiro wilk (P>0.05)	Levene (P>0.05)	Anova (P<0.05)
P1	3,80	0,866*		
P2	4,43	0,650*		
P3	2,74	0,099*	0,209**	0,024***
K+	3,34	0,296*		
K-	3,20	0,126*		

Table 2. Results of normality, homogeneity, and statistical comparison of neutrophil cells

Group	Mean	Shapiro wilk (P>0.05)	Levene (P>0.05)	Anova (P<0.05)
P1	2,50	0,82*		
P2	7,67	0,77*		
P3	6,17	0,33*	0,99**	0,001***
K+	6,67	0,96*		
K-	2,67	0,091*		

Table 3. Results of normality, homogeneity, and statistical comparison of lymphocyte cell

Group	Mean	Shapiro wilk (P>0.05)	Levene (P>0.05)	Anova (P<0.05)
P1	2,14	0,421*	0,833**	0,001***
P2	4,57	0,685*		

P3	1,66	0,389*
K+	1,17	0,106*
K-	0,63	0,059*

Group P2 (10% licorice extract) had the highest macrophage cell count (4.43), while Group P3 (15% licorice extract) had the lowest (2.74), suggesting that the best effect may occur at 10%. Table 1 shows the results for macrophage cell counts in five groups: three treatment groups (P1, P2, P3) and two control groups (K+ and K−). The analysis checked normality with the Shapiro–Wilk test and equal variances with Levene's test before using parametric tests. A one-way ANOVA was performed to see if there were significant differences among groups. These results show that raising licorice extract concentration does not always increase macrophage numbers.

The Shapiro–Wilk normality test yielded p-values greater than 0.05 ($P > 0.05$), indicating that the data were normally distributed across all groups. Therefore, the dataset met one of the key assumptions for conducting a parametric ANOVA. The Levene's test yielded a p-value of 0.209 ($P > 0.05$). This indicates that the variances among groups are homogeneous or exhibit equal variance, thereby fulfilling the second assumption required for conducting ANOVA. The ANOVA test yielded a p-value of 0.024 ($P < 0.05$). This indicates a statistically significant difference in macrophage counts across at least two treatment groups.

Table 2 presents the statistical analysis results for neutrophil cell counts across five experimental groups: three treatment groups (P1, P2, and P3) and two control groups (K+ and K−). The data analysis was conducted in three stages: normality testing using the Shapiro–Wilk method to assess whether the data were normally distributed, homogeneity testing using Levene's test to ensure equal variance among groups, and ANOVA (Analysis of Variance) to determine the presence of statistically significant differences between the treatment and control groups. The mean neutrophil count in group P2 (medium-dose licorice extract) was the highest (7.67). Groups P1 and K- exhibited the lowest counts, approximately 2.5–2.7, indicating milder inflammatory activity. Group K+ also showed a relatively high neutrophil count (6.67), suggesting ongoing inflammation despite therapeutic intervention. Overall, administration of licorice extract influenced neutrophil cell numbers, particularly at a specific concentration (P2).

The normality test yielded p-values > 0.05, indicating that the data were normally distributed. Thus, the dataset met the first ANOVA assumption. Levene's test for homogeneity yielded a p-value of 0.99, also above 0.05, indicating homogeneous variances among groups and satisfying the second ANOVA assumption. The ANOVA test yielded a p-value of 0.001 (< 0.05), indicating a significant difference in neutrophil counts between the treatment and control groups. Thus, licorice extract at varying doses alters neutrophil dynamics, suggesting distinct biological responses at different concentrations.

Table 3 presents the statistical analysis of lymphocyte counts across five experimental groups: three treatment groups (P1, P2, and P3) and two control groups (positive/K+ and negative/K−). The analysis was conducted in three stages: normality testing with the Shapiro–Wilk test, homogeneity testing with Levene's test, and significance testing with ANOVA. The mean values revealed that Group P2 (10% licorice extract) had the highest lymphocyte count (4.57), followed by P1 (2.14), P3 (1.66), K+ (1.17), and K− (0.63).

The Shapiro–Wilk test results (P1 = 0.421; P2 = 0.685; P3 = 0.389; K+ = 0.106; K− = 0.059) indicated all groups had p-values greater than 0.05, confirming normal distribution. Levene's test yielded a p-value of 0.833

(>0.05), suggesting homogeneous variances among groups. The ANOVA test then produced a p-value of 0.001 (<0.05), indicating a statistically significant difference in lymphocyte counts between treatment and control groups. These findings suggest that administration of 10% licorice extract elicited a stronger immune response than other doses and controls, while the lower lymphocyte counts in Groups K+ and K− may reflect a milder immune response or a resolving inflammatory process.

DISCUSSION

Phytochemical analysis of licorice extract (*Glycyrrhiza glabra L*) revealed the presence of key bioactive compounds, namely flavonoids and saponins, in high concentrations. These compounds are known for their significant pharmacological activities, including anti-inflammatory, immunomodulatory, and wound healing properties. This finding provides a strong scientific rationale for the use of licorice extract in herbal-based research and therapeutic applications.

Group P2 (10% licorice extract) demonstrated the highest mean macrophage cell count, indicating that this concentration was the most effective in stimulating macrophage activity during the wound healing process. Furthermore, group P2 showed the highest neutrophil count compared to the other groups, indicating a stronger inflammatory response at this concentration. In contrast, Group P1 and the positive control group (K+) showed lower neutrophil counts, suggesting milder inflammatory activity or that the tissue healing process in these groups had progressed to a more advanced stage relative to the others. Moreover, the 10% dose demonstrated the most optimal effect in stimulating the immune response, as evidenced by the highest increase in lymphocyte cell counts compared to other doses and control groups.

Previous research by Hanafi et al. showed that licorice extract significantly accelerates wound healing. In a study with Guinea pigs, 10% licorice extract cream increased epidermal formation, collagen deposition, and neovascularization, leading to faster wound healing compared to the control group.[18] Licorice extract promotes re-epithelialization and increases collagen synthesis, which are crucial for wound closure and tissue repair.[18,19]

This study found that 10% licorice extract was most effective in healing traumatic ulcers compared to 5% and 15% extracts, as measured by the expression of macrophages, neutrophils, and lymphocytes. These results indicate that increasing the extract concentration does not always correlate with the desired effect. Several studies have shown that herbal medicines can function through a hormesis mechanism, where low doses can stimulate adaptive responses, while high doses can inhibit or even cause toxic effects.[20–22] For example, low doses of certain phytochemical compounds can enhance cellular defense systems and immune function, while high doses can induce cytotoxic or anti-inflammatory responses.[22] Studies have shown that the dose-effect relationship of herbal medicines can vary. Increasing the dose can enhance the effect up to a certain point, after which the effect may decrease or even become negative effect.[23,24] Using doses exceeding recommended limits can cause serious side effects.[25]

Glycyrrhizin is the primary saponin in licorice, known for its anti-inflammatory and immunomodulatory properties.[26] Glycyrrhizin inhibits the production of reactive oxygen species (ROS) by neutrophils, which play a key role in inflammation and may contribute to tissue damage. The flavonoids in licorice, including liquiritigenin, liquiritin, and isoliquiritigenin, are recognized for their antioxidant and anti-inflammatory properties.[27] Licorice compounds inhibit inflammatory pathways, including NF-κB and MAPK. This inhibition reduces the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6.[14] Licorice also modulates immune cell activity,

increasing leukocyte counts and phagocytic activity, which are crucial for wound healing and infection control.[19] The antioxidant properties of flavonoids and saponins in licorice reduce oxidative stress, further aiding the healing process.[28,29] Licorice flavonoids and saponins neutralize free radicals, which helps reduce oxidative damage and support cellular health.[28] This analysis supports licorice's use in herbal research and therapy.

Lipopolysaccharide (LPS) activates M1 macrophages, which then produce pro-inflammatory cytokines such as TNF-α and IL-6.[30] Glycyrrhizin and licorice flavonoids significantly inhibit the secretion of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) in LPS-stimulated macrophages, which helps reduce inflammation and tissue damage.[31] Besides that, flavonoids promote M2 macrophage differentiation. They also enhance the production of anti-inflammatory cytokines such as IL-10.[32,33] This shift helps in resolving inflammation and promoting tissue repair.

Previous research has shown that licorice can promote the proliferation of T and B cells in the whole blood of mice, potentially through the IL-17 signalling pathway.[34] Furthermore, licorice flavonoids can suppress ion channel activity in T-lymphocytes, which is crucial for their activation and function, potentially providing therapeutic benefits for immune-related diseases.[35] Licorice polysaccharides, especially those of low molecular weight, stimulate T lymphocyte proliferation. They also enhance immune responses by increasing cytokine levels, including IL-2, IL-6, and IL-7.[36,37]

A limitation of the research conducted was the lack of comparison between days when testing the effectiveness of licorice extract on healing oral ulcers. Therefore, further research should provide input for researchers to test effectiveness based on differences in observation days.

CONCLUSION

Based on the study titled *Effectiveness of Licorice Extract (Glycyrrhiza glabra L.) on Traumatic Ulcer in Mice with Parameter Study: Macrophage Cells, Neutrophil Cells, and Lymphocyte Cells*, it can be concluded that Licorice extract (*Glycyrrhiza glabra L.*) enhances the healing of traumatic oral ulcer by modulating inflammatory and immune response, particularly through the activity of macrophages, neutrophils and lymphocytes, which support key processes such as debris phagocytosis, inflammation regulation, fibroblast stimulation, and epithelial regeneration, ultimately accelerating wound healing. Moreover, the study demonstrates that the 10% licorice extract concertation provides the most effective therapeutic outcome compared to the 5% and 15% concentrations as well as both positive and negative control groups.

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