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THE EFFECT OF ETHANOLIC EXTRACT OF MISWAK STEMS (SALVADORA PERSICA) ON THE HEALING OF POST-EXTRACTION SOCKETS IN WISTAR RATS (RATTUS NORVEGICUS)

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Abstract

The high prevalence of post-extraction complications, such as delayed wound healing and suboptimal bone regeneration, underscores the importance of effective therapeutic interventions. This study evaluated the efficacy of ethanolic extract of Miswak stems (Salvadora persica) in accelerating post-extraction socket healing in Wistar rats. The study involved two groups: the intervention group treated with 50% S. persica extract and the control group treated with distilled water. Each group consisted of 16 samples, with clinical and histopathological evaluations conducted on the fifth-day post-extraction. The methodology included topical application of S. persica extract on extraction sockets under controlled laboratory conditions, followed by clinical assessments using the Inflammatory-Proliferative-Remodeling (IPR) scoring system and histopathological analysis of osteoblast density. Results showed significantly improved clinical healing scores (mean IPR: 7 vs. 6 in the control group) and higher osteoblast density in the intervention group, indicating accelerated bone remodeling and tissue repair. Statistical analysis (Mann-Whitney and paired sample t-test) confirmed the effectiveness of the extract ($p < 0.05$). These findings suggest that S. persica extract effectively enhances oral wound healing and bone regeneration, likely due to its bioactive compounds with anti-inflammatory and osteogenic properties. Further studies are required to evaluate its safety and long-term efficacy for clinical applications.

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INTRODUCTION

Post-extraction socket healing is crucial in ensuring the oral cavity's health, function, and aesthetics. This process involves a complex interaction of biological mechanisms, including inflammation, proliferation, and remodeling, regulated through cellular and molecular mediators. The balance between these phases ultimately determines

the quality and speed of healing. This process's imbalance can result in complications such as delayed healing, infection, or alveolar bone loss, which may hinder subsequent dental rehabilitation. Therefore, optimizing post-extraction healing is a cornerstone in dental research and clinical practice.

To improve therapeutic strategies, attention has shifted toward natural compounds that offer regenerative and antimicrobial properties. *Salvadora persica*, commonly known as the toothbrush tree or "miswak," has gained attention for its potential applications in dentistry. Traditionally used for oral hygiene in many cultures, *Salvadora persica* possesses biological properties such as antimicrobial, anti-inflammatory, and osteogenic activities, which theoretically enhance wound healing and tissue regeneration. However, the application of *Salvadora persica* in post-extraction socket healing remains underexplored, particularly regarding its effects on osteoblast activity, a critical factor in bone remodeling, and clinical parameters such as wound closure and inflammation.

Existing literature provides a solid foundation for investigating *Salvadora persica*. Studies by Aljarbou et al. (2022) and Mekhemar et al. (2021) highlight its ability to inhibit oral pathogens and modulate inflammatory responses. Additionally, its ethanolic extract has been shown to promote osteoblast proliferation in vitro, suggesting its potential to enhance alveolar bone regeneration. However, most of these studies focus on isolated cellular models or antimicrobial tests, leaving a gap in understanding its clinical relevance in vivo. Research on post-extraction socket healing offers a unique opportunity to evaluate the broader impact of *Salvadora persica* on soft tissue and bone healing in physiological contexts.

This study addresses the need for in vivo evidence on the therapeutic efficacy of ethanolic extract of *Salvadora persica* in post-extraction socket healing. Using a controlled experimental design, the study aims to evaluate the effects of *Salvadora persica* on two primary parameters: the clinical progression of wound healing and the quantitative enhancement of osteoblasts, which are crucial for bone formation and socket stabilization. These results provide direct measures of healing while offering insights into the biological mechanisms influenced by the extract.

The significance of this study extends beyond the context of post-extraction care. As biocompatible and patient-friendly interventions gain acceptance in modern dentistry, these findings could pave the way for integrating *Salvadora persica* into mainstream dental practice. Furthermore, elucidating its role in improving clinical and cellular outcomes, this research contributes to the growing evidence supporting plant-based therapies in regenerative medicine.

It is essential to note the broader implications of this study. If proven effective, the ethanolic extract of *Salvadora persica* could serve as a cost-effective and accessible alternative to conventional pharmacological agents, particularly in resource-limited settings where access to advanced dental care is restricted. Additionally, its natural origin aligns with the global push toward sustainable healthcare solutions, making it an attractive candidate for further development.

METHODS

This study employed a laboratory-based experimental approach to investigate the effect of ethanolic extract of *Salvadora persica* on post-extraction socket healing and its

impact on osteoblast proliferation in Wistar rats (Rattus norvegicus). The research was conducted from May to September 2023 at the Pharmacy Laboratory of Universitas Muslim Indonesia.

The study design followed a Post-Test Only Control Group Design, dividing 32 Wistar rats into two groups: one group was treated with 50% ethanolic extract of *Salvadora persica*, and the other served as a control, treated with distilled water. Subject selection criteria included male Wistar rats weighing 200–250 grams and aged 2–3 months. Rats with anatomical abnormalities, previous experimental use, or missing teeth were excluded. Ethical standards were adhered to, including humane euthanasia practices during sample collection.

The materials used in the study included *Salvadora persica* stems, 96% ethanol, distilled water, and histological reagents such as 10% formalin and hematoxylin-eosin stain. Equipment included surgical instruments, microscopes, and extraction tools such as a rotary evaporator and macerator. The extraction process for *Salvadora persica* was systematic: fresh stems were chopped, dried in an oven at 50–60°C, and ground into powder. The powder was macerated with 96% ethanol for several days, followed by filtration and evaporation to produce a concentrated extract. This extract was diluted with distilled water to a 50% concentration for experimental use.

The experimental procedure involved clinical and histological evaluations. Over five days, clinical observations were conducted using the Inflammatory-Proliferative-Remodeling (IPR) scoring system, which assessed parameters such as granulation tissue, flap closure, and hematoma. On the fifth day, the rats were euthanized with a lethal dose of ketamine, and mandibular samples were collected for histological analysis. To count osteoblasts, these samples were processed, decalcified, stained, and examined under a microscope. In the intervention group, post-extraction sockets were treated with 50% ethanolic extract of *Salvadora persica* using a cotton bud, while the control group received the same treatment with distilled water.

The sample size was calculated using Federer's formula to ensure adequate statistical power. With two groups and a minimum requirement of 16 rats per group, 32 rats were included in the study. Data analysis was performed using SPSS version 26. Independent t-tests were used to compare IPR scores and osteoblast counts between groups, while one-way ANOVA evaluated within-group variations during the observation period.

The primary outcomes of the study focused on two aspects. First, clinical healing was assessed using IPR scores. Second, histological analysis evaluated osteoblast activity to determine the extract's effect on bone formation. Ethical standards were maintained throughout the study, including proper handling and burial of animal remains post-experimentation.

RESEARCH RESULTS

Clinical Healing Scores (IPR)

Post-extraction socket healing was evaluated in two groups: the intervention group treated with *Salvadora persica* (50%) extract and the control group treated with distilled water. Observations indicated significantly faster healing in the intervention group. Table 1

below presents the average IPR (Inflammatory, Proliferative, Remodeling) scores on the fifth day.

Table 1. Average IPR Scores on Day 5

Group	Average IPR Score (Day 5)
Intervention	7
Control	6

These results indicate that the intervention group achieved better healing outcomes than the control group, suggesting that *Salvadora persica* influences the reduction of inflammation and enhances the proliferative and remodeling phases during healing. This clinical difference is visualized in Figure 1, which compares the average IPR scores on the fifth day.

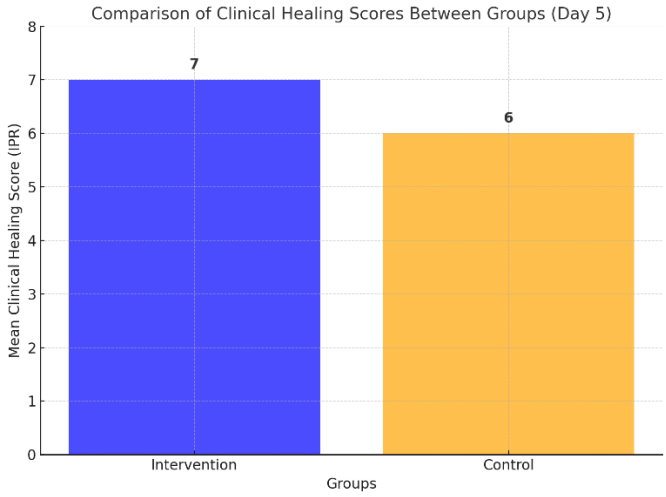


Figure 1. Comparison of Clinical Healing Scores Between Intervention and Control Groups on Day 5

The intervention group showed significantly higher average scores, reflecting accelerated healing. Statistical analysis using the Mann-Whitney U test, as shown in Table 2, confirmed these findings.

Table 2. Mann-Whitney U Test Results for IPR Scores

Group	Mean Rank	Mean Total Score	p-value
Intervention	1.55	0.506	0.000
Control	1.33	0.418	

The p-value (<0.05) indicates a statistically significant difference between the two groups. The higher IPR scores in the intervention group support the effectiveness of *Salvadora persica* in enhancing post-extraction socket healing.

Osteoblast Count

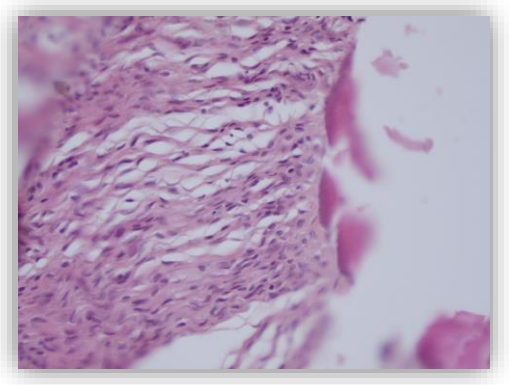
The frequency of osteoblasts, a critical indicator of bone regeneration, was analyzed histologically. The intervention group showed more osteoblasts than the control group, as presented in Table 3.

Table 3. Osteoblast Frequency in Control and Intervention Groups

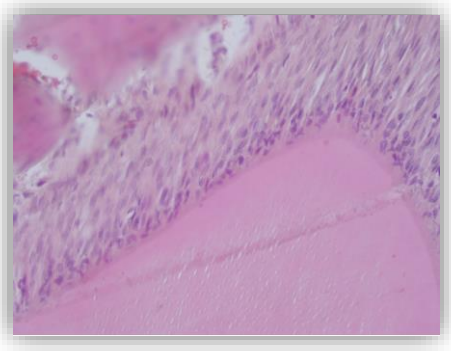
Group	Osteoblast Count	Frequency (n)	Percentage (%)
Control	45	4	25.0
	46	2	12.5
	47	4	25.0
	48	1	6.3
	50	3	18.8
	51	2	12.5
	Total		16
Intervention	49	4	25.0
	50	6	37.5
	51	2	12.5
	52	3	18.8
	54	1	6.3
	Total		16

The intervention group exhibited higher osteoblast density, particularly in the range of 50–52, indicating faster bone regeneration.

Control Group VS Intervention Group



Control Group



Intervention Group

Figure 2. Histological Comparison of Osteoblast Density

A paired t-test was performed to evaluate the significance of the difference in osteoblast count. The results are shown in Table 4.

Table 4. Paired t-Test Results

Variable	Mean	Standard Deviation	p-value
Pre-Post	-34.78	13.64	0.000

The significant p-value (<0.05) confirms the influence of *Salvadora persica* extract in enhancing osteoblast activity and bone healing.

The results of this study provide robust evidence of the regenerative potential of *Salvadora persica* (Miswak) stem extract in supporting oral wound healing, particularly in post-extraction sockets. The improved clinical healing scores and osteoblast density in the intervention group demonstrate the efficacy of this extract. These findings align with previous literature emphasizing the osteogenic and anti-inflammatory properties of *S. persica*. The flavonoids, tannins, and other bioactive compounds in this plant are believed to mediate these effects by modulating cellular activities involved in bone remodeling (8). Furthermore, the high osteoblast activity observed in the intervention group indicates that *S. persica* not only accelerates healing but also enhances bone quality through improved osteogenesis.

The findings support the hypothesis that *S. persica* promotes osteoblast differentiation and proliferation, as demonstrated in prior in vitro studies (8). This mechanism may be attributed to the phytochemical profile of *S. persica*, including flavonoids and fluoride, which stimulate osteoblast formation and inhibit osteoclast activity (9). In this study, the intervention group exhibited better clinical healing scores (mean IPR score of 7 compared to 6 in the control group) and higher osteoblast density, reflecting faster healing and better tissue organization, critical for successful post-extraction recovery.

Limitations and Challenges

Despite its promising results, this study has several limitations. The short observation period of five days may not encompass the long-term process of bone remodeling. Bone healing is a complex process involving initial inflammation, proliferation, and advanced remodeling, which requires weeks to months for full completion. Therefore, these results likely reflect only the early phases of healing, leaving the long-term implications of *S. persica* use unexplored.

Additionally, the lack of more diverse control groups, such as a placebo group or comparisons with standard pharmacological treatments (e.g., chlorhexidine), limits the comparative analysis. Future studies should include these controls to validate the efficacy of *S. persica* against conventional wound-healing agents. Variability in wound-healing responses among subjects could also introduce bias, necessitating larger sample sizes in subsequent research.

Potential risks related to the safety profile of *S. persica* extract should also be considered. Although no side effects were reported in this study, long-term use might pose risks of systemic effects due to bioaccumulation or interactions with other medications. Therefore, toxicological assessments and dose optimization studies should be prioritized to establish comprehensive safety guidelines.

Future Research Directions

To build upon these promising findings, future research should consider several factors. First, longer observation periods are required to evaluate the long-term effects of *S. persica* extract on bone healing and its potential in preventing complications such as dry sockets or delayed healing. Second, studies involving human subjects in randomized clinical trials are essential to assess translational application and effectiveness in diverse populations. Third, molecular investigations into specific pathways modulated by *S. persica*, such as its role in regulating cytokines, growth factors, and osteogenesis-related genes, could provide deeper insights into its mechanisms of action.

Moreover, comparisons with other natural and synthetic wound-healing agents would contextualize the therapeutic potential of *S. persica* in modern clinical practice. Its compatibility with existing dental materials, such as bone grafts and guided tissue regeneration membranes, should also be explored. The development of standardized formulations, such as topical gels or mouthwash solutions, could facilitate its integration into routine dental care.

CONCLUSION

This study provides compelling evidence that ethanolic extract of *Salvadora persica* significantly enhances clinical healing and osteoblast activity in post-extraction sockets. The intervention group demonstrated better healing outcomes compared to the control group, as evidenced by higher IPR scores and increased osteoblast density. These findings highlight the therapeutic potential of *S. persica* in oral wound healing and bone regeneration. The bioactive components of *S. persica* play a critical role in promoting healing through anti-inflammatory, antibacterial, and osteogenic mechanisms. Considering its affordability, natural origin, and effectiveness, *S. persica* holds promise as a sustainable alternative to synthetic wound-healing agents. However, further research is necessary to evaluate its long-term safety, optimize dosing, and confirm its clinical efficacy through human trials.

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