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Effect of *Hypericum perforatum* on Early Wound Healing after Tooth Extraction: A Randomized Controlled Clinical Trial

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A B S T R A C T

Objectives: *Hypericum perforatum* (*H. perforatum*) has natural anti-inflammatory properties when used as a dressing on ulcers and burn wounds. The aim of this study was to investigate the effect of topical application of hydroethanolic gel of *H. perforatum* on soft tissue healing in tooth extraction sockets.

Materials and Methods: This split-mouth randomized controlled clinical trial was performed on 30 patients aged 18-30 years who required simultaneous extraction of maxillary premolars bilaterally for orthodontic reasons. After tooth extraction, 2mL of 3% *H. perforatum* gel was injected into the extraction socket in the intervention side. Pain was measured based on a Numeric Rating Scale (NRS). Socket healing was assessed using the standardized Landry, Turnbull, and Howley index. Repeated measures ANOVA and generalized estimating equations (GEE) were employed to compare different indices between the two groups (alpha=0.05).

Results: The mean age of the participants was 23.53 years. Of all, 25 were females and 5 were males. The intervention side had a significantly lower pain than the control side ($P<0.05$). The wound size decreased at 3 and 7 days, and it was smaller in the intervention side than the control side ($P<0.05$). The healing index score was significantly higher in the intervention side than the control side ($P<0.001$).

Conclusion: The results showed that 3% *H. perforatum* hydroethanolic gel was effective for promoting soft tissue healing in tooth extraction sockets, decreasing pain, and improving the wound healing index.

Keywords: *Hypericum perforatum*; Wound Healing; Tooth Extraction

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INTRODUCTION

Wound healing includes a series of cellular and biochemical processes in response to the incurred injury to improve tissue function. Naturally, the injured tissues genetically have a healing power and regeneration potential. Nonetheless, a wide range of internal and external factors can accelerate or delay the wound healing process (1). Wound healing following tooth extraction is by secondary intention, and involves three stages of inflammation, proliferation, and remodeling. Normally, immediately after tooth extraction, the inflammatory phase begins, which has a vascular and a cellular component (1). In the vascular phase, contraction of the injured vessels decreases the blood flow, and induces hemostasis and clot formation. In the cellular phase, presence of serum complements, cytokines, and growth factors secreted at the

site of injury leads to chemotaxis of macrophages and neutrophils, and stimulation of mitogenic signaling in fibroblasts. The proliferation phase begins from day 4 with the migration of immature fibroblasts and angiogenesis. In the proliferation phase, the granulation tissue becomes rich in collagen fibers and cells, and provides a connective tissue matrix for tissue regeneration (2). In some cases, wound healing can be accelerated by interventions such as prescribing mouthwashes, antibiotics, or topical medications (3).

In recent years, because of the side effects of chemical drugs, attempts have been made to use plant-based compounds and their derivatives to accelerate healing of extraction sockets at both cellular and molecular levels (4-6).

Hypericum perforatum L. (*H. perforatum*) from the Hypericaceae family, known as the St. John's wort, is a plant with a rich history. It is currently one of the most widely used herbal medicines worldwide (7, 8). *H. perforatum* has been widely investigated in clinical and in vitro studies, for which, in addition to antidepressant effects, numerous bioactive activities have been noted including anti-inflammatory (7), wound healing (9-13), antioxidant (11), antibacterial(8, 11), and antiviral (14) properties. In 2009, the European Herbal Medicine Product Committee approved the use of *H. perforatum* topical drugs for symptomatic treatment of mild skin inflammations and wound cleansing (7). This product has also been incorporated in the London pharmacopeia as Hyperici oleum (11). The commonly utilized hydroalcoholic extract of *H. perforatum* contains bioactive compounds including hypericin, hyperin, tannins, amentoflavone, hyperforin, xanthones, and flavonoids (7). Three important compounds responsible for the therapeutic effects of the hydroalcoholic extract of *H. perforatum* include hyperforin, hypericin, and flavonoids, constituting about 1-5%, 0.3%, and 2-4% of the hydroalcoholic extract, respectively (7). Hyperforin is the most abundant lipophilic compound in the composition of *H. perforatum* hydroalcoholic extract (15); which, in addition to offering anti-inflammatory and antibacterial effects, also contributes to wound healing by stimulating the differentiation of keratinocytes and recovery of the injured tissue (10, 11, 16). Furthermore, the *H. perforatum* extract is the main source of hypericin, which exerts its anti-inflammatory effects by inhibiting the cytokines secreted from macrophages such as interleukin-12 (11).

Topical application of *H. perforatum* alone or in combination with other drugs has been suggested to control dental pain and alleviate post-extraction pain (7). Furthermore, its prophylactic application for pain control before and after tooth extraction and dental surgery has shown promising results in reducing pain and inflammation after 48 hours. The anti-inflammatory properties of *H. perforatum* seem to contribute to alleviation of acute and chronic pain, and increasing the pain perception threshold (17).

An experimental study on rats showed that application of *H. perforatum* extract after tooth extraction improved the clinical and histopathological outcomes (18). Also, clinical evidence supports the effects of local and systemic application of *H. perforatum* on healing of oral lesions (19, 20).

The wound healing and anti-inflammatory properties of *H. perforatum* are among its known effects; however, in comparison to its antidepressant effects and other central nervous system activities, the aforementioned properties have remained understudied. Controlled clinical trials on topical use of *H. perforatum* alone at suitable doses seem to be essential. Considering the scarcity of studies in this regard as well as the high safety level and availability of *H. perforatum*, the present study was performed to investigate the effect of topical application of hydroethanolic gel of *H. perforatum* on soft tissue healing of tooth extraction sockets.

MATERIALS AND METHODS

Trial Design and Changes After Trial Commencement

This study was a randomized, controlled, double-blind, split-mouth clinical trial. The protocol received ethical approval from the Institutional Ethics Committee of Kurdistan

University of Medical Sciences (IR.MUK.REC.1401.228) and was registered prospectively in the Iranian Registry of Clinical Trials (IRCT20210113050025N1). The trial was conducted from October 2020 to August 2021. No changes were made to the methods after trial commencement.

Participants, Eligibility Criteria, and Settings

A total of 30 patients (aged 18-30 years) requiring bilateral extraction of maxillary premolars for orthodontic reasons were recruited via convenience sampling from the outpatient clinic. They received necessary information about the study objectives and signed written informed consent forms. Then, their demographic information was collected using a checklist. The inclusion criterion was the need for bilateral extraction of maxillary premolars for orthodontic reasons. Patients with a history of local or systemic disease, history of any drug allergy, pregnant and lactating women, women with a history of oral contraceptive use, smokers, and patients requiring antibiotics or non-steroidal anti-inflammatory drugs after the treatment were excluded from the study.

Preparation of the H. perforatum Hydroethanolic Gel

The dried powder of *H. perforatum*, standardized to contain 0.08% total hypericin, was procured from Dineh Pharmaceutical Company (Tehran, Iran). A tissue-compatible gel containing the plant extract was formulated in the Pharmacology Laboratory of Babol University of Medical Sciences as follows:

To prepare the biogel, 95cc of distilled water was transferred to a 500mL flask. Then, Chitosan (1g; Merck KGaA, Darmstadt, Germany) was dissolved in the mixture by the addition of acetic acid (500 µL; Merck KGaA). Following the addition of Carbopol (0.2g; Merck KGaA), the solution was heated. Subsequently, methylparaben and propylparaben (Merck KGaA, Darmstadt, Germany) were dissolved in 95% alcohol and added to the previous solution along with 0.3wt% of the extract. Eventually, 2mL of glycerin (Merck KGaA, Darmstadt, Germany) was added to the sample, and the hydroethanolic gel of 3% *H. perforatum* extract was ultimately prepared.

Surgical procedure

Prior to tooth extraction, all patients were instructed to perform a 30- seconds oral rinse with 0.2% chlorhexidine gluconate (Behsa Pharmaceutical Co., Iran). Local anesthesia was administered using 2% lidocaine with 1:100,000 epinephrine (Darupakhsh Pharmaceutical Co., Tehran, Iran). Next, maxillary premolars were extracted bilaterally under local anesthesia by a specialist using the standard conventional method. Extractions were simply performed by forceps. Following extraction, on the intervention side, the socket was filled with 2mL of 3% *H. perforatum* gel via syringe until it was level with the surrounding soft tissue. On the control side, the socket was irrigated with sterile saline only. A sterile gauze pad was then placed over both sockets, and patients were instructed to maintain pressure for 45 minutes. No sutures were placed in either group. Standard postoperative oral hygiene instructions were provided.

Outcomes

Pain was assessed using a Numeric Rating Scale (NRS) (Fig. 1).

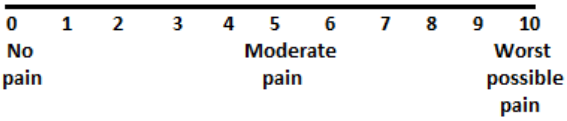

Fig 1. Numeric Rating Scale

Participants rated their pain intensity on a scale from 0 (no pain) to 10 (worst imaginable pain) at 2 hours, and at 3 and 7 days' post-extraction. Wound size was determined by measuring the buccolingual and mesiodistal dimensions with a Castroviejo caliper (Tarah Tajhiz Co., Tehran, Iran). The final size was calculated by multiplying the measured numbers. Healing was assessed using the Landry, Turnbull, and Howley index (Table 1) (21). Socket dimensions were measured twice to ensure data reliability. To maintain acceptable intra-examiner reliability, any discrepant measurements were repeated, and the average of the two most consistent values was recorded as the final result.

Table 1. Landry, Turnbull, and Howley healing index

Healing index	Very poor (1)	Poor (2)	Good (3)	Very good (4)	Excellent (5)
Tissue color	≥ 50% of gingiva red	≥ 50% of gingiva red	≥ 25% and < 50% of gingiva red	<25% of gingival red	All tissue pink
Response to palpation	Bleeding	Bleeding	No bleeding	No bleeding	No bleeding
Granulation tissue	Present	Present	None	None	None
Incision margin	Not epithelialized, with loss of epithelium beyond incision margin	Not epithelialized, with connective tissue exposed	No connective tissue exposed	No connective tissue exposed	No connective tissue exposed

Furthermore, no changes were made to the trial outcomes following the commencement of the study.

Sample Size Calculation

The sample size was calculated using the following formula, based on a 95% confidence level and 90% power.

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

Based on the standard deviation (σ) and mean (μ) values reported in previous studies (22) , the minimum required sample size was calculated to be n = 13. To increase statistical power and ensure the robustness of the findings, a sample size of 30 participants was ultimately selected.

Interim Analysis and Stopping Guidelines

No interim analysis was planned or conducted for this trial.

Randomization

The allocation of intervention and control sides was determined using a table of random numbers. A two-digit number was randomly selected: if the number was even, the right quadrant was assigned as the intervention side and the left as the control; if the number was odd, the left quadrant was designated as the intervention side and the right as the control.

Blinding

As the maxillary premolars needed to be extracted bilaterally, one side was randomly selected as the intervention, and the other as the control side. In the intervention side, 2mL of 3% *H. perforatum* gel was used, while in the control side, the extraction socket was only washed with saline. Bilateral tooth extraction and gel application were performed by an orthodontist. To ensure double-blinding during follow-up sessions, a coded system was used to identify the intervention and control sides, keeping the patients and researchers unaware of the allocation.

Data were analyzed using SPSS 20 and a p-value less than 0.05 was considered statistically significant. Repeated measures ANOVA and generalized estimating equations (GEE) were employed to compare different indices between the two groups.

RESULTS

This study was performed on thirty 18- to 30-year-old patients who required extraction of their maxillary premolars for orthodontic reasons. The mean age of the participants was 23.53±4.64 years; 25 patients (83.3%) were females and 5 (16.7%) were males.

Pain:

Figure 2 presents the mean severity of pain at different time points. Pain severity was lower in the intervention group compared to the control group at all three time points. Although the difference in pain intensity at different times was significant within each group (P<0.05), repeated measures ANOVA showed no significant difference between the two groups in this regard (P=0.06).

Wound size:

The results regarding wound size are presented in Figure 3.

Wound size was smaller in the intervention group compared to the control group at all three time points. Although the difference in wound size at different times was significant within each group (P<0.05), repeated measures ANOVA showed no significant difference between the two groups in this regard (P=0.07).

Tissue color change at the extraction site:

The results regarding tissue color change at the extraction site are provided in Table 2. The GEE results revealed that the odds of normal gingival color were higher in the intervention group than in the control group (odds ratio=0.25, P=0.002), and the odds ratio was higher on day 7 than on day 3 (odds ratio=6.51, P<0.001).

Bleeding on palpation:

The GEE results showed that the odds of bleeding on palpation were higher in the control group than the intervention group but not significantly (odds ratio=2.44, P=0.09), and the odds of bleeding on palpation were lower at 7 days than 3 days (odds ratio=0.052, P<0.001, Table 3).

Presence of granulation tissue:

The GEE results showed that the odds of presence of granulation tissue were higher in the control group than the intervention group but not significantly (odds ratio=2.44, P=0.09), and the odds of presence of granulation tissue were lower at 7 days than 3 days (odds ratio=0.052, P<0.001, Table 4).

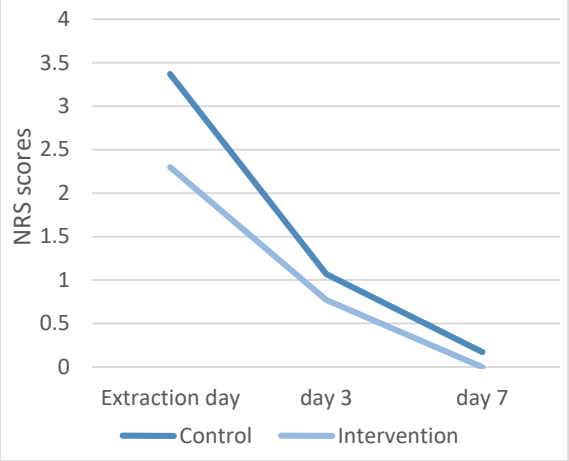

Fig 2. Comparison of pain score between the intervention and control sites (trend of change in pain score)

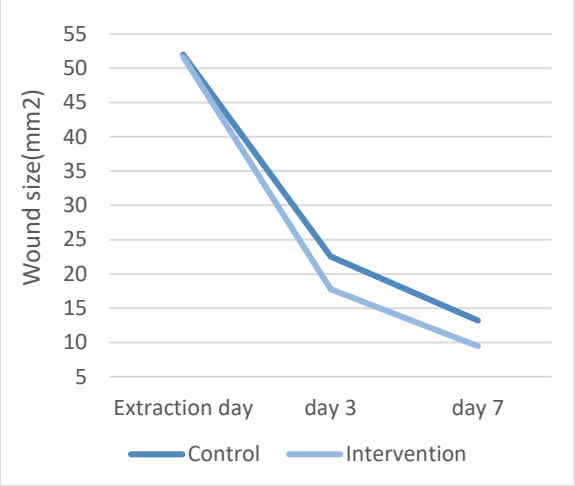

Fig 3. Comparison of wound size (mm^2) between the intervention and control sites

Table 2. Comparison of tissue color between the intervention and control sites

Time	Tissue color	Group		Total
		Control	Intervention	
Day 3	≥ 50% of gingiva red	13 (61.9%)	8 (38.1%)	21
	≥ 25% and < 50% of gingiva red	9 (52.9%)	8 (47.1%)	17
	<25% of gingival red	8 (42.1%)	11 (57.9%)	19
	All tissue pink	0 (0%)	3 (100%)	3
Day 7	≥ 50% of gingiva red	2 (100%)	0 (0%)	2
	≥ 25% and < 50% of gingiva red	12 (80%)	3 (20%)	15
	<25% of gingival red	13 (46.4%)	15 (53.6%)	28
	All tissue pink	3 (20%)	12 (80%)	15
	Day: OR=6.51 (P<0.001) Group: OR=0.25 (P=0.002)			

OR: Odds ratio

Gingival margin epithelialization:

The GEE results showed that the odds of gingival margin epithelialization were lower in the control group than the intervention group but not significantly (odds ratio=0.40, P=0.09), and the odds of gingival margin epithelialization were higher at 7 days than 3 days (odds ratio=16.67, P<0.001, Table 5).

Wound healing score:

The results related to the wound healing score are presented in Table 6. Repeated measures ANOVA showed that the wound healing index was significantly different between the two groups (P<0.001), and wound healing score in the intervention group was higher than that in the control group.

Table 3. Comparison of response to palpation between the intervention and control sites

Time	Response to palpation	Group		Total
		Control	Intervention	
Day 3	Bleeding	14 (60.9%)	9 (39.1%)	23
	No bleeding	16 (43.2%)	21 (56.8%)	37
Day 7	Bleeding	2 (100%)	0 (0%)	2
	No bleeding	28 (48.3%)	30 (51.7%)	58
	Day: OR=0.052 (P<0.001) Group: OR=2.44 (P=0.09)			

OR: Odds ratio

Table 4. Comparison of granulation tissue formation between the intervention and control sites

Time	Granulation tissue	Group		Total
		Control	Intervention	
Day 3	present	14 (60.9%)	9 (39.1%)	23
	None	16 (43.2%)	21 (56.8%)	37
Day 7	Present	2 (100%)	0 (0%)	2
	None	28 (48.3%)	30 (51.7%)	58
	Day: OR=0.052 (P<0.001) Group: OR=2.44 (P=0.09)			

OR: Odds ratio

Table 5. Comparison of gingival margins between the intervention and control sites

Time	Gingival margin	Group		Total
		Control	intervention	
Day 3	Epithelialized	17 (43.6%)	22 (56.4%)	39
	Not epithelialized	13 (61.9%)	8 (38.1%)	21
Day 7	Epithelialized	28 (48.3%)	30 (51.7%)	58
	Not epithelialized	2 (100%)	0 (0%)	2
	Day: OR=16.67 (P<0.001) Group: OR=0.40 (P=0.09)			

OR: Odds ratio

Table 6. Comparison of wound healing score between the intervention and control sites

Time	Group	Mean ± SD
Day 3	intervention	3.23± 0.94
	Control	2.73± 0.78
Day 7	intervention	4.27± 0.69
	Control	3.53± 0.78
Group: F=11.67, df=1 (P=0.001)		

DISCUSSION

This study evaluated the effect of hydroethanolic gel of *H. perforatum* extract on soft tissue healing of tooth extraction sockets, and indicated a reduction in pain and enhanced wound healing process. Wound healing is the normal response of the injured tissue, which includes inflammatory, proliferation, and remodeling phases. Inflammation is the first stage following injury (10). Reduction of inflammation is the first step in accelerating healing. Evidence shows that resolution of inflammation in addition to pain reduction lowers the risk of infection and accelerates the healing course (10, 17). The results of the present study indicated that the extent of inflammation and the wound margin redness (tissue color) were significantly lower in the intervention group compared to the control group. Furthermore, the level of pain was lower in the intervention group. *H. perforatum* herbal extract contains compounds making it suitable for resolution of inflammation (23). Flavonoids such as hyperforin and hypericin are among the bioactive compounds typically found in the hydroalcoholic extract of *H. perforatum* (10, 16, 23, 24).

The hyperforin present in the *H. perforatum* extract has good bioavailability and reduces the inflammatory responses by suppressing the signaling pathways and modulating the processes involved in chronic and acute inflammation. Furthermore, it diminishes oxidative burst in polymorphonuclears. It has been shown that hyperforin can induce long-term changes in the signaling pathway and cell transcription even after extraction from the cell culture medium following an incubation period (10, 23). Studies have shown that *H. perforatum* extract and hyperforin contribute to the inhibition of cyclooxygenase-1 enzyme, prostaglandin E2, 5-lipoxygenase, arachidonic acid, and interleukin-10, and resolution of inflammation (10, 24, 25). Furthermore, the hyperforin and flavonoids present in the *H. perforatum* extract are antibacterial, and, possibly by creating a barrier against microbial contamination at the beginning of the healing period, they contribute to shortening of the inflammation phase and acceleration of wound healing. The *H. perforatum* aqueous extract has been proven effective for inhibiting the Gram-positive bacteria, especially methicillin-resistant Staphylococcus aureus (24).

Hypericin also possesses anti-inflammatory effects and causes a significant reduction in cytokines secreted in response to the stimulation of macrophages (11). Menegazzi et al. (23) indicated that *H. perforatum* extract protects cells by reducing the production of inflammatory mediators and oxygen free radicals as well as regulating the pH equilibrium. A clinical study demonstrated the notable effects of topical application of *H. perforatum* on resolution of pain and inflammation after dental surgery (17). Samadi et al. (26) observed that topical use of *H. perforatum* ointment three times a day for 16 days minimized wound pain and itching compared to the control group. In the present study, application of 3% *H. perforatum* hydroethanolic extract gel diminished wound size and improved healing in the intervention group at 3 and 7 days, compared to the control group. The proliferation phase starts 3 and 4 days after injury with increased migration of fibroblasts, and lasts for 2-3 weeks. Fibroblasts play a key role in healing and closure of wounds because of their migration and collagen synthesis (27). Suntar et al. (10) studied in vivo excision and incision wound models and observed that application of *H. perforatum* extract once a day increased the migration of fibroblasts and induced the synthesis of collagen bundles by affecting the proliferation phase. The *H. perforatum* extract contains antioxidant flavonoid compounds, which can induce vascularization, reduce cell necrosis, and enhance the viability of collagen fibrils by inhibiting lipid peroxidation (10).

Ozturk et al. (27) investigated the effect of *H. perforatum* alcoholic extract on the healing process in chicken embryonic fibroblasts culture medium at the cellular level. They indicated increased migration of fibroblasts, stimulation of collagen bundle synthesis, improved tissue regeneration, and proliferation of epithelial cells. It appears that the bioactive compounds present in *H. perforatum* extract contribute to acceleration

of wound healing by stimulating the activity of fibroblasts, producing collagen, and differentiating keratinocytes (27). Also, *H. perforatum* improves the functional organization of the epidermis by stimulating the differentiation of keratinocytes in the damaged epidermis and formation of a cornified envelope (11).

Yadollah-Damavandi et al. (12) examined full-thickness skin wounds in diabetic female rats. They found that topical application of *H. perforatum* increased the number of fibroblasts and synthesis of collagen bundles, and enhanced revascularization compared to the control group. Samadi et al. (26) revealed that *H. perforatum* ointment topically applied three times a day within a 16-day period on caesarean section wounds accelerated wound healing and diminished scarring on day 10 compared to the control group.

Lavagna et al. (9) indicated that clinical application of a mixture of *H. perforatum* and *Calendula arvensis* oil was effective for improving epithelial regeneration, diminishing the wound size, and enhancing wound healing. Yucel et al, (13) clinically evaluated the effect of *H. perforatum* oily extract on pressure sore wounds of patients hospitalized in the intensive care unit macroscopically and histopathologically. The results showed that its application twice a day for 40 days reduced the wound size and significantly improved pressure sore wounds. Altan et al. (24) evaluated the histopathological and biochemical effects of topical application of *H. perforatum* oil twice a day on wounds induced in the palate of diabetic rats. The results showed enhanced epithelialization of mucosal wounds and a reduction in number of polymorphonuclear leukocytes on day 7. Unlike the results of Altan et al., (24) no significant difference was observed in the present study between the test and control groups regarding the response to palpation, epithelialization, or granulation tissue formation. Differences in the results may be explained by differences in methodology since Altan et al. (24) applied *H. perforatum* extract on the wound site twice a day for 7 days. Motallebnejad et al. (19) showed that application of *H. perforatum* extract in the form of mouthwash (0.5%) was effective for reducing pain and acceleration of recovery. Sardella et al. (20) evaluated the efficacy of systemic administration of 300 mg capsules containing *H. perforatum* extract in patients with burning mouth syndrome, and reported a general reduction in the number of sites with reported burning sensation, although it failed to decrease the pain score of patients with burning mouth syndrome.

As no clinical study to date has investigated the effect of *H. perforatum* extract on the soft tissue of tooth extraction sockets, the present study provided new information about the effects of topical application of hydroethanolic gel of *H. perforatum* extract on wound healing in tooth extraction sockets.

Since the study's follow-up period was limited to 7 days, which only captures the early inflammatory and proliferative phases of wound healing, further studies are needed to evaluate the effect of *H. perforatum* gel on the later remodeling stage of healing and its final outcome.

CONCLUSION

The findings of this study demonstrate that the topical application of *H. perforatum* hydroethanolic extract significantly promoted wound healing and reduced pain following tooth extraction. Given this promising efficacy and the plant's rich profile of bioactive compounds, further investigations are warranted to elucidate the precise underlying mechanisms of its wound-healing action.

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CONFLICT OF INTEREST STATEMENT

None declared.

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