The effectiveness of 50% Cocor Bebek (Kalanchoe pinnatta) leaf extract on clinical appearance of post teeth extraction sockets in Wistar rats: a laboratory experimental study

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ABSTRACT

Introduction: One of the most common procedures performed in dental clinics is tooth extraction. Post-extraction, a wound known as a socket is formed. Inflammation is a fundamental response to the wound after tooth extraction, which subsequently progresses to the tissue repair process, involving the replacement of dead cells with living cells from fibrous tissue. An alternative material that can be used in this healing process is the Kalanchoe pinnata leaf. This study aimed to analyze the effectiveness of 50% Kalanchoe pinnata leaf extract on the clinical appearance of post-extraction sockets in Wistar rats. **Methods:** This research employed a laboratory experimental method using a Posttest Only Control Design, conducted on 32 Wistar rats divided into two groups: a control group and a treatment group, which received 50% Kalanchoe pinnata leaf extract. Observations were carried out on days 5, 14, and 42 in both groups using the Inflammatory Proliferative Remodeling (IPR) scale, and statistical analysis was performed using the Mann-Whitney test. **Results:** The results of the difference analysis using the Mann-Whitney test showed a p-value of 0.000 ($p<0.05$), indicating a significant difference in effectiveness between the treatment and control groups. **Conclusion:** Based on the study findings, the clinical appearance of post-extraction sockets in Wistar rats on days 5, 14, and 42 following the application of 50% Kalanchoe pinnata leaf extract demonstrated a positive impact on wound healing.

Keywords

cocor bebek (Kalanchoe pinnata) leaf extract, wound healing, tooth extraction

Efektivitas ekstrak daun cocor bebek (Kalanchoe pinnata) 50% terhadap tampakan klinis soket pasca pencabutan gigi pada tikus Wistar: studi eksperimental laboratoris

ABSTRAK

***Pendahuluan**: Salah satu prosedur yang paling sering dilakukan di klinik adalah pencabutan gigi. Pasca pencabutan gigi akan menghasilkan perlukaan yang disebut soket. Inflamasi adalah respon dasar terhadap adanya luka pasca pencabutan gigi yang akan berlanjut ke proses perbaikan jaringan yaitu penggantian sel mati oleh sel hidup dari jaringan fibrosa. Bahan alternatif yang dapat digunakan yaitu daun cocor bebek (Kalanchoe pinnata). Tujuan penelitian untuk menganalisis efektivitas ekstrak daun cocor bebek (Kalanchoe pinnata) 50% terhadap tampilan klinis soket pasca pencabutan gigi pada tikus wistar. **Metode**: Penelitian ini menggunakan metode Eksperimental Laboratoris yaitu pengujian yang dilakukan di laboratorium dengan bentuk penelitian berupa post test only control design pada hewan coba tikus wistar sebanyak 32 ekor yang dibagi menjadi 2 kelompok yaitu kelompok kontrol dan kelompok perlakuan yang diberikan ekstrak daun cocor bebek (Kalanchoe pinnata) 50%. Kemudian dilakukan pengamatan pada kelompok kontrol dan perlakuan hari ke-5, 14, dan 42 menggunakan skala Inflammatory Proliferative Remodeling (IPR) dan diuji menggunakan uji statistik Mann-Whitney. **Hasil**: Berdasarkan hasil uji perbedaan menggunakan Mann-Whitney, menunjukkan bahwa p-value=0,000 ($p<0,05$). Hal ini menunjukkan terdapat perbedaan efektivitas yang signifikan antara kelompok perlakuan dan kontrol. **Simpulan:** Berdasarkan hasil penelitian tampakan klinis soket pasca pencabutan gigi tikus wistar pada hari ke-5, 14, dan 42 setelah diberikan ekstrak daun cocor bebek (Kalanchoe pinnata) 50% memiliki dampak penyembuhan yang baik.*

Kata kunci

ekstrak daun cocor bebek, penyembuhan luka, pencabutan gigi

INTRODUCTION

One of the most frequently performed procedures in dental clinics is tooth extraction.[1] Tooth extraction is a surgical procedure that involves both soft and hard tissues of the oral cavity.[2] The most common reasons for tooth extraction include dental caries, besides caries there are periodontal diseases, supernumerary teeth, impacted teeth, teeth that can no longer be treated with endodontics, teeth that are involved in cysts and tumors, teeth that are involved in jaw fractures. Ideally, tooth extraction is the removal of an intact tooth or tooth root without causing pain, with as little trauma as possible to the supporting tissue so that the wound from the extraction will heal normally and not cause complications.[3]

According to the 2018 Basic Health Research (RISKESDAS) as many as 57.6% of the Indonesian population experienced dental health problems with dental and oral health problems in Indonesia being dental caries, which was 45.3%. The prevalence of dental caries in Indonesia increased by 35.6% from 53.2% in 2013 to 88.8% in 2018.[4]

Wound healing is influenced by the ability of cells to return to their normal structure through cell growth or regeneration. The wound healing process can be accelerated under certain conditions. Factors that can affect wound healing include hormones, stress, obesity, medication use, smoking, nutrition, systemic disease, alcohol, and age. [5,6,7]

A socket is the wound left after a tooth extraction.[8] Inflammation is a fundamental response to this wound, which progresses into tissue repair, involving the replacement of dead cells with living cells from fibrous tissue.[9] Fibroblasts play a crucial role in wound healing.[5] Their proliferation is essential, as they release growth factors that promote tissue repair by synthesizing reticular fibers, collagen, amorphous extracellular substances, and elastic fibers. [10]

The inflammatory phase (days 3–5 post-surgery) begins immediately after the injury and lasts until approximately the fifth day. This phase consists of two sub-phases: early inflammation (hemostasis phase) and late inflammation phase. When tissue injury occurs, severed blood vessels lead to bleeding, triggering a hemostatic response. During this process, platelets (thrombocytes) are released in response to the contact between blood and collagen and extracellular matrix, initiating clot formation.[11]

The late inflammatory phase serves to eliminate necrotic tissue and prevent microbial colonization or infection. Once hemostasis is achieved, acute inflammatory cells and neutrophils invade the affected area to eliminate debris and bacteria. This immune response is characterized by cardinal symptoms of inflammation: tumor (swelling), calor (heat), rubor (redness), dolor (pain), and functio laesa (loss of function). During this phase, the wound is temporarily stabilized by a weak fibrin matrix. Following inflammation, the proliferation phase initiates tissue repair.[12]

The proliferation phase (day 14 post-surgery) is marked by the formation of pink granulation tissue containing inflammatory cells and collagen secretion. Clinically, this phase presents as re-epithelialization, pink tissue coloration, and scar formation. Dysregulation of this phase may lead to excessive collagen deposition and tissue contracture.[13]

The remodeling phase (six weeks post-surgery) aims to balance matrix degradation (removal of weaker type II collagen) with matrix formation (replacement with stronger type I collagen). Collagen fiber homeostasis and extracellular matrix remodeling are regulated by serine proteases and matrix metalloproteinases (MMPs). Clinically, this phase is characterized by normalized tissue coloration and scar maturation. Disruptions in this balance may result in excessive matrix degradation or inadequate remodeling, leading to keloid scars or wound dehiscence.[13]

Kalanchoe pinnata (Cocor Bebek) contains terpenoids, saponins, tannins, steroids, and flavonoids.[14] The presence of saponins, flavonoids, and tannins contributes to wound

healing by acting as antioxidants and antimicrobials, which promote tissue repair and accelerate epithelialization. Additionally, bufadienolides found in Kalanchoe pinnata exhibit insecticidal, anticancer, and antitumor properties.[15]

To date, no studies have evaluated the effectiveness of 50% Kalanchoe pinnata leaf extract on the clinical appearance of post-extraction sockets in Wistar rats. This study aimed to analyze the effectiveness of 50% Kalanchoe pinnata leaf extract on the clinical appearance of post-extraction sockets in Wistar rats.

METHODS

This study has been approved by the Health Research Ethics Commission of the Muslim University of Indonesia and the Ibn Sina Hospital YW-UMI. This study was a laboratory experimental study using a posttest only control design. Randomization was conducted by marking the Wistar rats using a natural dye on their tails and forelimbs before assigning them to either the treatment group or the control group. This randomization process used simple random sampling and ensured that the rats in each group had uniform characteristics, minimizing potential bias.

Based on the sample size calculation using Federer's formula, a total of 32 Wistar rats were required and divided into two groups: 16 rats in the treatment group, which received 50% Kalanchoe pinnata leaf extract after the extraction of the first mandibular incisor, and 16 rats in the control group, which did not receive 50% Kalanchoe pinnata leaf extract after undergoing the same tooth extraction procedure.

The inclusion criteria for the study subjects were male Wistar rats with healthy oral mucosal soft tissues, a body weight of 200–250 g, an age of 2 to 3 months, and in good health, as indicated by active movement. The equipment used in this study included masks and gloves for handling the Wistar rats, an electrical blender, extraction containers, rotary evaporator, maceration tools, analytical balance, filter paper, glass jars, Wistar rat cages, food and water containers, extraction forceps (elevator), 1.0 cc syringe, smartphone camera, work pads, cotton buds, and pens. The materials used in this study included 50% Kalanchoe pinnata leaf extract, 96% ethanol (as a solvent), ketamine (as an anesthetic), cotton, food and drinking water for the Wistar rats, and 32 printed copies of the Inflammatory Proliferative Remodeling (IPR) assessment scale.

The process of preparing Kalanchoe pinnata leaf extract began with thoroughly washing 2 kg of fresh Kalanchoe pinnata leaves, which were then cut into smaller pieces and air-dried at room temperature for seven days. Once dried, the leaves were ground into a fine powder using an electrical blender. The powdered leaves were then macerated with 96% ethanol, covered, and left to stand for 24 hours. Afterward, the solvent was evaporated using a rotary evaporator until a thick extract was obtained. To prepare the 50% concentration extract, 0.5 g of the thick extract was measured using an analytical balance and dissolved in 1 ml of ethanol, resulting in a 50% Kalanchoe pinnata extract.

The preparation of 50% Kalanchoe pinnata leaf extract was conducted at the Pharmacy Laboratory, Pharmacognosy and Natural Materials Division, while the Wistar rat treatment was carried out in the Pharmacology Department of Universitas Muslim Indonesia. The Wistar rats were housed in cages with adequate air circulation and lighting, protected from direct sunlight and noise to ensure a calm environment. Food was provided ad libitum, consisting of fiber-rich foods, tubers, corn, and green vegetables, given every morning and evening. Drinking water was supplied through bottles with feeding pipes. The Wistar rats underwent a one-week adaptation period to acclimate to their environment.

In the treatment group, Wistar rats were lightly anesthetized via 0.2 ml ketamine injection and observed until anesthesia took effect. The left mandibular incisor was then extracted using rotation movement with extraction forceps. Following the extraction,

50% Kalanchoe pinnata leaf extract was applied to the post-extraction socket using a cotton bud while the rats were still under anesthesia. Once the effects of anesthesia wore off, the rats were provided food and water to maintain their health.

In the control group, Wistar rats were lightly anesthetized via 0.2 ml ketamine injection and observed until anesthesia took effect. The left mandibular incisor was then extracted using rotation movement with extraction forceps. After the effects of anesthesia wore off, the rats were provided food and water to maintain their health.

Clinical healing assessment was conducted on days 5, 14, and 42 post-extraction using the Inflammatory Proliferative Remodeling (IPR) scale, which was printed and completed based on the condition of each experimental subject. In the IPR scale, the inflammatory phase was evaluated 3–5 days after tissue injury based on eight parameters, measured on a 9-point scale (0–8), including bleeding (spontaneous or on palpation), granulation tissue, hematoma, tissue color, incision margin, pus, edema, and pain. A score of 5–8 indicated a successful inflammatory phase. The proliferative phase was evaluated 14 days after tissue injury based on five parameters, measured on a 6-point scale (0–5), including re-epithelialization, tissue color, scarring, pus, and pain. A score of 3–5 indicated successful healing. The remodeling phase was evaluated six weeks after tissue injury, based on three parameters, measured on a 4-point scale (0–3), including scar formation, tissue color, and pain. A score of 2–3 indicated successful healing. The total IPR scale score ranged from 0 to 16, where 0–4 indicated poor healing, 5–10 indicated acceptable healing, and 11–16 indicated excellent healing.

The collected data were subjected to a normality test. If the data were normally distributed, the independent t-test was applied. However, if the data were not normally distributed, analysis was performed using the Mann-Whitney test. In this study, a data normality test was carried out, but the results were not normally distributed, so for further testing, the Mann-Whitney statistical test was used.

RESULTS

The healing process of post-extraction socket wounds in both the treatment group and control group of Wistar rats was observed on days 5, 14, and 42 using the Inflammatory Proliferative Remodeling (IPR) scale. The collected data were analyzed to compare wound healing between the groups, as illustrated in Figure 1.

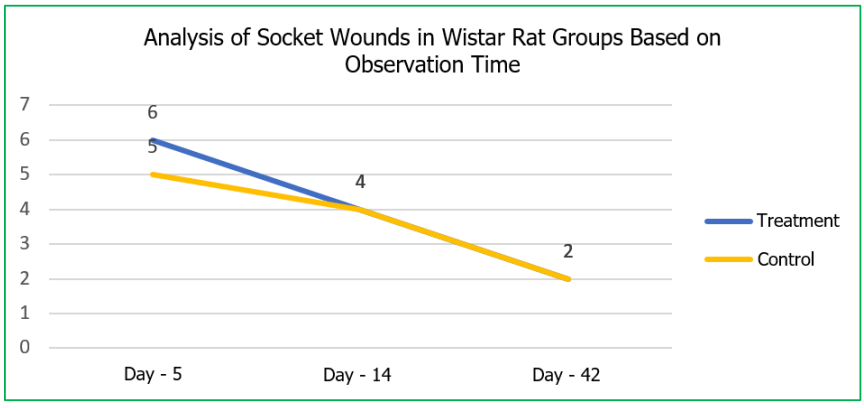

Figure 1. Average socket wound scale in Wistar rats based on observation time

Based on Figure 1, the analysis results on the effectiveness of 50% Kalanchoe pinnata leaf extract were obtained. In the treatment group, on day 5, the average socket wound scale was 6, indicating a successful inflammatory phase. On day 14, the average

socket wound scale was 4, indicating a successful proliferative phase. Finally, on day 42, the average socket wound scale was 2, indicating a successful remodeling phase.

In the control group, on day 5, the average socket wound scale was 5, indicating a successful inflammatory phase. On day 14, the average socket wound scale was 4, indicating a successful proliferative phase. Finally, on day 42, the average socket wound scale was 2, indicating a successful remodeling phase. Overall, based on the longest observation period, the socket wound scale decreased in both groups.

The clinical observation data on post-extraction socket appearance in both groups were tested for normality using the Shapiro-Wilk test ($p>0.05$), as shown in Table 1.

Table 1. Normality test results for the treatment and control groups

Variabel	*P-value*
Inflammatory Proliferative Remodeling (Treatment Group)	0.001
Inflammatory Proliferative Remodeling (Control Group)	0.001

Based on the data, both the treatment and control groups had a p-value of 0.000 ($p<0.05$), indicating that the data were not normally distributed. Therefore, statistical analysis was conducted using the Mann-Whitney test, as shown in Table 2 .

Table 2. Mann-Whitney test results comparing the effectiveness of 50% Kalanchoe pinnata leaf extract and the control group

Group	Mean	Mean Total IPR Score	*P-value*
Treatment Group (50% Kalanchoe pinnata Leaf Extract)	22.75	11.75	0.000
Control Group	10.25	10.75	

The test results showed that the average total IPR score was 11.75 in the treatment group (50% Kalanchoe pinnata extract) and 10.75 in the control group. The Mann-Whitney test yielded a p-value of 0.001 ($p<0.05$), indicating a significant effect on socket wound healing between the treatment and control groups. The group that received 50% Kalanchoe pinnata extract exhibited better healing scores compared to the control group.

DISCUSSION

This study was designed to determine the effectiveness of 50% *Kalanchoe pinnata* leaf extract on the clinical appearance of post-extraction sockets in Wistar rats. The part of Kalanchoe pinnata used in this study was the leaf, which contains terpenoids, saponins, tannins, steroids, and flavonoids.

Kalanchoe pinnata is a succulent plant originating from Madagascar, capable of thriving in dry environments and found in tropical regions such as Hawaii, Asia, Australia, New Zealand, India, and even Poland. [16] This plant is known for its unique reproductive method, which occurs through buds and leaves (adventitious buds).[17]

According to a study by Fakhrurrazi,[18] *Phyllanthus acidus (L.) Skeels* (ceremai leaf) was found to promote the healing of oral mucosal wounds in Wistar rats, due to its flavonoid, alkaloid, and steroid content. Alkaloids possess antimicrobial properties, which help accelerate wound healing. Similarly, the flavonoids in *Kalanchoe pinnata* act as anti-inflammatory agents, inhibiting inflammatory mediators in a manner similar to non-steroidal anti-inflammatory drugs (NSAIDs). Flavonoids also have antioxidant and antibacterial properties. The antioxidant mechanism of flavonoids in wound healing works by inducing the cellular antioxidant system and increasing glutathione concentrations by approximately 50% in the body. Meanwhile, tannins play a role in enhancing wound contraction during the healing process. Tannins act as astringents, which shrink skin pores, harden tissues, halt exudation and mild bleeding, cover wounds,

and prevent bleeding complications, thereby accelerating epithelialization.[18]

Observations of post-extraction sockets in Wistar rats treated with 50% Kalanchoe pinnata leaf extract showed more effective mucosal healing compared to the control group, which did not receive the extract. This aligns with a study conducted by Zahra (2017), which found that *Kalanchoe pinnata* leaves possess wound-healing activity, with the treatment group healing faster than the control group.[19]

Wound healing is an organism's response to tissue or organ damage, and an effort to return it to a homeostatic state in which the skin tissue remodeling process is determined by the formation of a functioning epithelium that covers the wound and can produce physiological stabilization of the tissue or organ.[20]

Future applications of *Kalanchoe pinnata* leaf extract may serve as a hemostatic agent for patients with bleeding disorders. However, further research is needed, particularly on systemic bleeding disorders, toxicity tests, and clinical trials, especially for its use in dental surgery.[21] In this study, there was limited time to care for and feed the experimental animals so that their body weight met the requirements for being an experimental animal in the study.

CONCLUSION

The clinical appearance of post-extraction sockets in Wistar rats treated with 50% *Kalanchoe pinnata* leaf extract demonstrated a positive impact on wound healing. The implication of this study suggests that *Kalanchoe pinnata* can be utilized as a herbal remedy for promoting post-extraction socket wound healing.

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