Effectiveness of robusta coffee bean extract gel (C*offea Canephora*) on the thickness of collagen fibers after wistar rat tooth extraction

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ABSTRACT

***Background**: Tooth extraction causes injury to the alveolar bone and oral mucosa which is followed by the body 's natural response through wound healing. One of the important parameters and indicators of wound healing is collagen density. Collagen is synthesised by fibroblasts in the proliferative phase, which was formed from day 3 and reached its peak on day 7. Robusta coffee beans have active compounds in the form of anti-inflammatory and antioxidants that are effective in accelerating wound healing. Objective: To determine the effectiveness of robusta coffee bean extract gel (Coffea canephora) at concentrations of 12,5%, 25%, and 50% in increasing the thickness of collagen fibres in socket wound healing after tooth extraction in Wistar rats.*

***Method:** This type of research is laboratory experimental. The samples used were 40 male Wistar rats divided into 5 groups: negative control, positive control, 12.5% robusta coffee bean extract gel treatment, 25% robusta coffee bean extract gel treatment, and 50% robusta coffee bean extract gel treatment. The sample group was decapitated on the 3rd and 7th day after tooth extraction. Socket tissues were taken to make histological preparations stained with trichrome mallory and then measured using Adobe Photoshop CS 6.0 software.*

***Results**: The average thickness of collagen fibres in the Robusta coffee bean extract gel treatment group was higher than that in the control group (p<0,05).. The 50% Robusta coffee extract gel concentration group was more effective in increasing the number of collagen fibres than the 12.5% and 25% concentration groups..*

***Conclusion**: Robusta coffee bean extract gel could increase the thickness of collagen in wound healing after tooth extraction.*

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INTRODUCTION

Tooth extraction occupies the second top position, which is an action to overcome dental and oral problems, which is 7.9%, based on the results of Basic Health Research in 2018 in the field of dental and oral health [1] Tooth extraction or extraction is a procedure in which one or more than one tooth is removed from its socket, which can cause injury to the alveolar bone and oral mucosa. [2–4] Then naturally, the body will conduct the wound healing process. Wound healing is a process that involves cellular and biochemical responses both locally and systemically, which are divided into three main phases, namely the inflammatory, proliferative, and maturation phases. [5,6]

One of the important parameters and indicators in the wound healing process is collagen density. During the wound healing process, collagen is synthesised by fibroblasts in the proliferative phase formed from day 3. Collagen will appear in real quantity on day 7 after injury and begin to stabilise and organise around day 14. Collagen is a key protein in the connective tissue and plays an important role in wound healing with scar repair, and formation. The collagen formed forms connective tissue that connects the edges of the wound tightly. Collagen can also increase the linkage between new tissues, thus strengthening the healing area.[7 8 9]

Tooth extraction is successful if accompanied using a complete healing process. When this is not achieved, it will cause complications and complaints from sufferers. The incidence of complications after tooth extraction is still common at 2.6%–30.9%. Several risk factors can cause complications of tooth extraction including systemic diseases, patient age, tooth root condition, and disorders of the temporomandibular joint [10 11] A common complication after tooth extraction is *dry socket, with* an incidence rate of 0.5% to 5% in Indonesia. The incidence of *dry socket* is higher in mandibular molars by approximately 3%–38%, and reaches 45% for the third molar of the mandible. [11,12]

Dry socket is characterised by prolonged inflammation that can slow down the wound healing process. For some patients, wound healing after tooth extraction needs to be accelerated. Especially for orthodontic patients who require tooth extraction or in patients who want to make denture. [13]

Therefore, several anti-inflammatory drugs are used to reduce the possibility of complications and speed up the wound healing process after extraction, one of which is [14] *alvogyl* given topically.[12,15]

Alvogyl is a *dressing agent* after extraction consisting of various substances, including butamben, iodoform, and eugenol. However, *alvogyl* has a relatively expensive price, so it is less desirable by the public. The use of *alvogyl* also has several side effects, namely acute inflammation, persistent granulation tissue, and failure to form scar connective tissue in sockets treated with *alvogyl*. Therefore, some herbal ingredients began to be used as a substitute for chemical drugs because of their minimal side effects.[16] Some herbal plants can be used to speed up the wound healing process with minimal side effects, one of which is coffee. The type of

coffee plant widely cultivated in Indonesia is robusta coffee. [17–19]

Robusta coffee contains several active ingredients, including alkaloid compounds, flavonoids, saponins, tannins, caffeine, chlorogenic acid, and trigonelline. Caffeine has antioxidant activity that can improve wound healing by neutralising free radicals that arise during the wound healing process. Chlorogenic acid and flavonoids function as anti-inflammatory agents; therefore, the inflammatory reaction will last shorter and result in an immediate proliferative phase.[20,21] Chlorogenic acid and flavonoids can also stimulate macrophages to produce TGF-β. Saponins in robusta coffee beans can activate and synthesise TGF-β, as well as modify the expression of TGF-β receptors in fibroblasts. TGF-β plays a role in inducing fibroblasts to proliferate, migrate, and synthesise collagen to promote wound healing. [22–24]

Research conducted by Ermawati et al. (2021)[25] showed that robusta coffee bean extract gel with concentrations of 40%, 50%, and 60% was effective in increasing collagen fiber density in the wound healing process after gingivectomy in Wistar rats. Therefore, the authors were interested in examining the effect of robusta coffee bean extract gel on collagen thickness during the healing process after tooth extraction in Wistar rats at concentrations of 12.5%, 25%, and 50%.

Research Method

This research is a laboratory experimental research with *a post-test only control group design*. This research was approved by the Ethics Commission of the Faculty of Dentistry, University of Jember (No. 1432/UN25.8/KEPK/DL/2022. The research was conducted at the Pharmaceutical Laboratory of the Faculty of Pharmacy, University of Jember (UNEJ), the Biomedical Laboratory of the Faculty of Dentistry and the Histology Laboratory of the Faculty of Dentistry. The samples used were 40 male Wistar rats divided into five groups: negative control group (K-), positive control group (K +), robusta coffee bean extract gel treatment group 12.5% (P12.5%), robusta coffee bean extract gel treatment group 25% (P25%), and robusta coffee bean extract gel treatment group 50% (P50%). Each sample group was divided into 2 subgroups based on the day of observation, namely the 3rd and 7th days.

Making Robusta Coffee Bean Extract Gel

Samples of dried coffee beans are mashed into powder using a coffee chopper and, then weighed as much as 500 gram. Then, the sample was macerated in a 96% ethanol solution at a ratio of 1:5 for 72 h in a maceration jar. The jar is closed tightly and stirred twice a day (morning and evening) to make it homogeneous. The sample was philtreed using philtre paper, and ethanol was evaporated using a rotary evaporator at 30°C–40°C to produce a 100% concentrated extract. Gelling begins with making a gel base by developing 2 g of Na-CMC in 98 mL of water at 70 °C in a mortar and pestle for 15 min. Then, stir until the preparation is clear, homogeneous, and a gel mass is formed. Concentrated robusta coffee bean extract is put into a mortar containing a gel base to be mixed until homogeneous so that

a robusta coffee bean extract gel concentration of 12.5% (0.0125 g/mL) is formed,25% (0.025 g/mL), and 50% (0.05 g/mL)[25]

Experimental Animal Treatment

After adaptation for one week, extraction was performed on the molar teeth of one left lower jaw of the wistar rat. Wistar rats were anaesthetised using a mixture of 0.04–0.08 mL ketamine and 0.1 mL xylazine intramuscularly on their legs. Wistar rats are fixed on rat dental chairs, and the rat's teeth are separated from the surrounding tissue using a semicircular sonde. After the rat 's teeth are detached from the attachment, they are carefully removed using an excavator. The rat's teeth were then taken from the socket using the clamp artery. The tooth socket was irrigated using physiological solutions and dried with cotton pellets. After bleeding stopped, the wistar rats were given treatment. After bleeding stopped, the wistar rats were given treatment. Group I was not given any treatment as K, group II was given alvogyl as K+, group III was given 12.5% robusta coffee bean extract gel, group IV was given 25% robusta coffee bean extract gel, and group V was given 50% robusta coffee bean extract gel. Application is carried out by spraying robusta coffee bean extract gel on the socket using a disposable syringe that has been taken by a needle at a dose of 0.05 mL. After the treatment action, suturing is performed on the socket. Furthermore, wistar rats were euthanized on days 3 and 7 according to their respective subgroups.

Histological Preparation and Observation of Collagen Fibers

Tissue collection was performed by cutting the lower jaw of the posterior rat by exaggerating the tissue taken along 5 mm in the distal mesial part of the tooth socket in the sagittal direction. Subsequently, the tissue is fixed using 10% formalin buffer for 12-18 hours. Then, decalcification is performed using 10% formic acid for 14 to soften the tissue. Soft tissue is made histologically, which includes dehydration, clearing, impregnation, embedding, and tissue cutting. Tissue cutting is performed in the mesiodistal direction with a thickness of 6 µm. Furthermore, the preparations that have been made are stained with trichrome mallory.

Observation of collagen fibers using binocular microscopy on tooth socket preparations stained blue with 400x magnification in three fields of view, namely the mesial, distal, and central The calculation of collagen fibre thickness was performed by analysing photos of observations taken with the Optilab camera using Adobe Photoshop CS 6.0 software by looking at the number of collagen pixels. Adobe Photoshop CS 6.0 Application Use Stage Collagen thickness measurement using Adobe Photoshop CS application 6.0 with the following stages :a. The preparation was photographed using an Optilab camera with a magnification of 400x. b. Open the Adobe Photoshop CS 6.0 application. c. Open the image by clicking "File", then click "Open". Then select the image that will be used. d. Click the "Window" menu, select the "Histogram" submenu. e. In the "Channel" box, select "Blue." Then the mean value will appear. Mean value Blue is the number of dots or pixels that indicate thickness collagen fibers. [26]

The amount of collagen fiber thickness was obtained from the average number of collagen pixels in three fields of view.

RESULTS

Table 1. Calculation of the average thickness of collagen fibers and standard deviation in each group.

Group Sample	Day 3 $\bar{x}$ ± SD	Day 7 $\bar{x}$ ± SD
K-	175.08 ± 4.64	188.66 ± 5.81
K+	184.60 ± 7.09	199.76 ± 6.22
P12.5%	196.95 ± 5.43	212.65 ± 1.70
P25%	207.02 ± 4.53	219.91 ± 3.12
P50%	215.73 ± 1.43	231.29 ± 2.52

Information:

- K- : Negative control group (without therapy)
- K+ : Positive control group (therapy *alvogyl*)
- P12.5% : Robusta coffee bean extract gel treatment group 12.5%
- P25% : Robusta coffee bean extract gel treatment group 25%
- P50% : Robusta coffee bean extract gel treatment group 50%

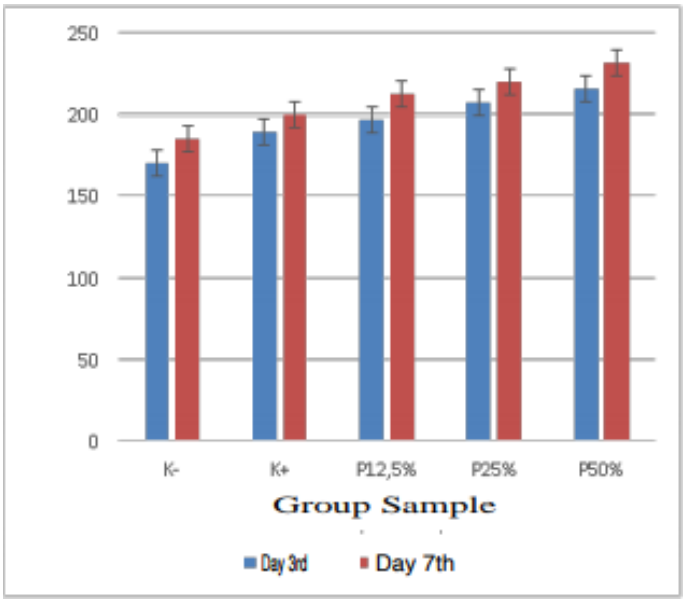


Figure 1. Diagram of the average thickness of the socket collagen fibers after tooth extraction in each group.

Based on the table and diagram above, the average thickness of collagen fibres on each observation day (day 3 and day 7) showed an increase in the treatment group compared with the control group (negative control and positive control). In addition, in each sample group, the average thickness of collagen fibers increased from day 3 to day 7. The average thickness of collagen fibers in the 50% robusta coffee bean extract the gel treatment group on day 7 had the highest average compared with the other groups. The lowest average collagen fiber thickness was in the negative control group on day 3.

Table 2. One way ANOVA test results

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	10910.879	9	1212.320	56.309	.000
Within Groups	645.899	30	21.530		

The results of *the One Way Anova test* obtained a significance of 0.000 ($p < 0.05$), indicating that there was a significant difference in the average amount of collagen fiber thickness between the sample groups.

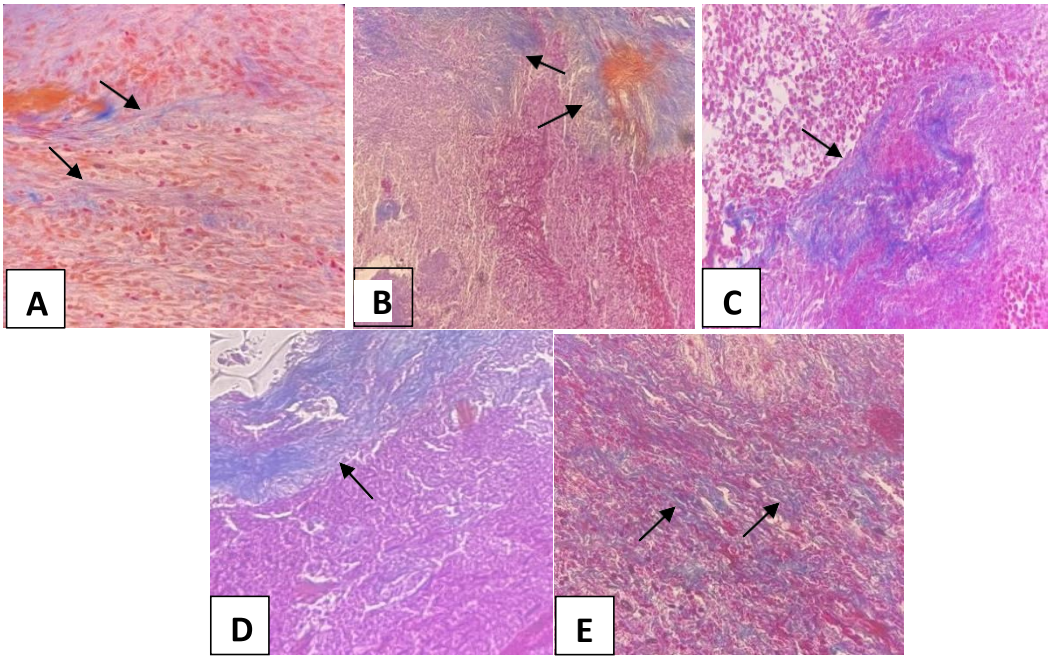
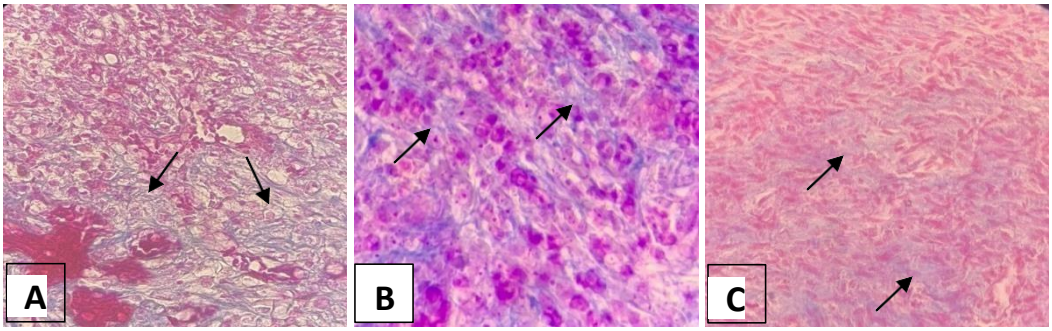


Figure 2. Histological images of collagen fibers on the 3rd day after tooth extraction. (A) negative control group, (B) positive control group, (C) 12.5% robusta coffee bean extract gel treatment group, (D) 25% robusta coffee bean extract gel treatment group, (E) 50% robusta coffee bean extract gel treatment group. (Black arrows indicate coloring collagen fibers *Trichrome Mallory* magnification 400x)



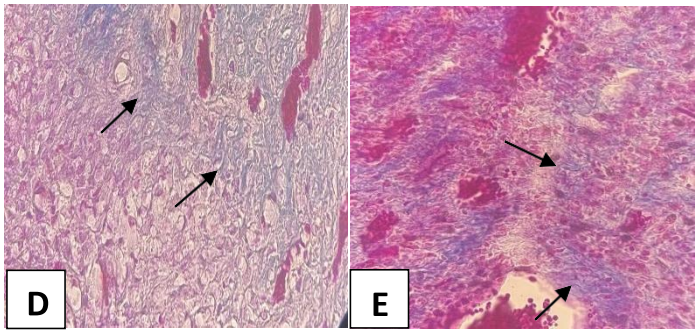


Figure 3. Histological images of collagen fibers on the 7th day after tooth extraction. (A) negative control group, (B) positive control group, (C) 12.5% robusta coffee bean extract gel treatment group, (D) 25% robusta coffee bean extract gel treatment group, (E) 50% robusta coffee bean extract gel treatment group. (Black arrows indicate coloring collagen fibers *Trichrome Mallory* magnification 400x)

DISCUSSION

The initial stage of the wound healing process after tooth extraction is the haemostasis and inflammatory phase. Shortly after tooth extraction, the alveolar socket will be filled with blood, platelet aggregation occurs, and blood clots form in the socket area. Platelet activation in the haemostasis phase releases several proinflammatory cytokines that provide chemomatic signals to inflammatory cells. The inflammatory phase is characterised by the migration of inflammatory cells to the wound area, followed by migrating neutrophil cells to perform phagocytosis. If the wound is not infected, the number of neutrophils decreases, and they are subsequently replaced by macrophages. Macrophages appear at 48–82 h and reach a peak on day 3 after tooth extraction, signifying that healing is entering the next stage, which is the proliferative phase. The proliferative phase is characterised by the migration of fibroblasts to the wound area. Fibroblasts appear significantly on day 3, and their number continues to grow until they reach their peak on day 7. As a result, fibroblasts become dominant cells on the 7th day after injury; therefore, the secretion of the extracellular matrix to add to the substance of the collagen matrix will also be dominant. Therefore, the average amount of collagen fiber thickness on day 7 has increased compared to day 3.[26,27] [3,7,28]

Histologically observed results showed that the 50% treatment group had the highest thickness of collagen fibers followed by the 25% treatment group, then the 12.5% treatment group. Similarly, in the treatment group euthanized on day 7. The difference in the thickness of collagen fibers at each treatment dose occurred because of differences in the concentration of robusta coffee bean extract gel given. The difference in the concentration of robust coffee bean extract gel affects the amount of active ingredient and the effectiveness of the gel in wound healing therapy. The higher the concentration level of robust coffee bean extract gel, the higher the active ingredient content.[29,30]

Active substances in robusta coffee beans also act as anti-inflammatory, including flavonoids and chlorogenic acid. The anti-inflammatory activity of chlorogenic acid inhibits cyclooxygenase enzymes. The anti-inflammatory activity of flavonoids works through the inhibition

of cyclooxygenase and lipoxygenase enzymes. The inhibition of these enzymes can reduce the production of prostaglandins and leukotrienes, thereby decreasing the migration of neutrophils in the inflammatory area This indicates that healing is entering the next stage, so the proliferation phase can occur immediately. Chlorogenic acid and flavonoids can also affect the secretion of IFN-γ which acts as an activator of macrophages. Active macrophages can produce [31,32] *growth factor* TGF-β which functions to induce fibroblast proliferation and migration and induces fibroblasts to synthesise collagen.[33]

Another active compound present in robusta coffee beans is saponins. Saponins can activate and synthesise TGF-β, and modify the expression of TGF-β receptors in fibroblasts. Saponins can increase the ability of fibroblast receptors to TGF-β, thereby increasing the ability of fibroblasts to bind to TGF-β. Saponins can also stimulate fibronectin synthesis, thereby accelerating the migration and proliferation of fibroblasts to the wound area. The synergistic effect of these compounds can increase the activity of fibroblasts to proliferate, migrate, and synthesise collagen to accelerate the healing of socket wounds after tooth extraction. [34,35,36] [37]

The results of the discussion above show that robusta coffee bean extract gel is an alternative medication treatment that is anti-inflammatory and antioxidant and can increase collagen thickness in wounds after tooth extraction with an optimal concentration of 50%. This medication can be given to patients with risk factors that can cause complications of tooth extraction, to orthodontic patients who require tooth extraction, or to patients who want to make dentures so that wound healing can be accelerated. The use of coffee bean extract gel is expected to be an alternative post-extraction healing besides the use of antibiotics.[38]

CONCLUSION

Based on the research that has been done, it can be concluded that topical administration of robusta coffee bean extract gel with a concentration of 50% can increase the thickness of collagen fibers in the socket wound healing process after wistar rat tooth extraction.

CONFLICT OF INTEREST

All authors declare that we have no conflicts of interest.

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