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The role of purple leaves extract (*Graptophyllum Pictum (L.) Griff*) on the number of fibroblasts and blood vessels in the socket after tooth extraction

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ABSTRACT

Background: *Tooth extraction is the process of removing teeth from the alveolus. It will leave a mark on the socket and surrounding soft tissue. One of the cells that plays an important role in the wound healing process after tooth extraction is fibroblasts. When an injury occurs, some blood vessels are damaged; therefore, new blood vessels need to form. Purple leaves extract could be an alternative treatment for wound healing after tooth extraction as it contains flavonoids, saponins, alkaloids, steroids, and tannins.* ***Purpose:*** *The study aimed to analyze the role of purple leaves extract on the increase in fibroblasts and blood vessels in the socket after tooth extraction in Wistar rats.* ***Methods:*** *The method used was a laboratory experiment with a post-test-only control group design. The samples used were 24 rats divided into two groups: the control group, which was given aquadest, and the treatment group, which was given 1.5 mL of purple leaves extract with 10% concentration by sondage. Tissue preparations were used to count fibroblasts, and blood vessels were counted and observed on the 3rd, 5th, and 7th days.* ***Results:*** *Statistical tests showed a significant difference in the number of fibroblasts and blood vessels between the control and treatment groups on days 3, 5, and 7.* ***Conclusion:*** *Purple leaves extract could increase the number of fibroblasts and blood vessels in the tooth socket after tooth extraction of Wistar rats.*

Keywords: *blood vessels; fibroblasts; purple leaves extract; tooth extraction*
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INTRODUCTION

The 2018 Basic Health Research found that 57.6% of Indonesia's population has dental and oral health problems, and tooth extraction was the second most used procedure to deal with it, with a percentage of 7.9%.[1] Tooth extraction is the process of removing a tooth from its socket.[2,3] Inadequate tooth extraction can lead to complications. Post-extraction complications due to considerable trauma can damage the alveolar bone in the tooth in question and affect the wound healing process in the area.[3–5]

The wound healing process consists of several phases: hemostatic, inflammatory, proliferative, and remodeling. The second phase, inflammation, is a process in which the body is injured and reaches its peak on the third day, which is marked by the presence of Polymorphonuclear (PMN), leukocytes, especially neutrophils and macrophages. The next phase, proliferation, is the formation of new blood vessels and granulation tissue, characterized by the migration of granulation cells, such as fibroblasts and endothelial cells. The remodeling phase is marked by the shrinking of the wound; in this phase, the maturation of collagen, epidermis, and tissue remodeling occurs; this phase typically lasts the longest.[6,7]

An important factor that helps accelerate the healing of damaged wounds, including those involving bone, is the formation of new vascularized tissue. Bone vascularization is triggered by the process of angiogenesis and several other factors. One of the factors that plays a significant role in bone vascularization is basic fibroblast growth factor (bFGF).

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It is through bFGF that fibroblasts play a role in shaping the walls of blood vessels. bFGF acts as an intermediary between the formation of vascularization in new bone and the differentiation of chondrocytes and osteoblasts that appear in the early phase of proliferation during the bone healing process.[4,6,7] bFGF is a growth factor that has the ability to induce stages in the angiogenesis process and is involved in wound repair and tissue development.[7,8] In tissue healing, bFGF is considered a growth factor that plays a role in stimulating endothelial proliferation, migration, and blood vessel formation. Together with platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), bFGF synergizes to accelerate new tissue formation.[4,8,9]

The tooth extraction process could cause injury to the tooth socket, damaging some blood vessels so that new blood vessels are needed.[9,10] The formation of new blood vessels is also one of the parameters for the success of the wound healing process.[4,11] The formation of new blood vessels plays a very important role in the wound healing process; new blood vessels could replace the damaged ones and supply nutrients to new cells formed in the wound tissue.[12] In addition, if, after tooth extraction, the wound fails in one of the healing phases, especially in the angiogenesis process, the wound cannot heal properly.[13]

Drugs can reduce complications and speed up the wound recovery process after tooth extraction. Complications may occur in inadequate tooth extraction. Some researchers argue that anti-inflammatory drugs are necessary for this condition. One of the non-steroidal anti-inflammatory drugs that is often used after tooth extraction is diclofenac. Nevertheless, previous studies reported that diclofenac administration could inhibit the formation of blood clots and fibroblasts;[12,13] therefore, an alternative drug to minimize the side effects of diclofenac administration is necessary. Purple leaves are known as plants with anti-inflammatory effects and have been reported to increase the number of fibroblasts in rats induced by *Porphyromonas gingivalis* in their sulcus.

Herbal medicines have started to be used instead of chemical ones for their minimal side effects.[13] One of the plants was purple leaves (*Graptophyllum pictum L. Griff*), developed from thirteen commodities by the Directorate General of Drug and Food Control as a leading medicinal plant. Empirically, people believe that purple leaves can heal wounds, usually by warming and attaching to the wound area. This plant contains active compound, such as alkaloids, flavonoids, saponins, and tannins.[14] Flavonoids in the purple leaves increase the growth factors needed during wound healing, including transforming growth factor-β (TGF-β), which could increase osteoblast[15] and the migration and proliferation of fibroblasts to the wounded area.[16] In addition, a 10% concentration was chosen so that 10% purple leaves extract could accelerate the wound recovery process in Wistar rats by increasing the number of fibroblasts and osteoblast of rats induced by *Porphyromonas gingivalis*.[15,16] Furthermore, this study aimed to analyze and elaborate on the role of purple leaves extract in increasing the amount of fibroblasts and blood vessels on the socket after tooth extraction of male Wistar rats.

MATERIALS AND METHODS

This research has been approved by the Ethics Committee Faculty of Dentistry, University of Jember, with letter number 118/PL17.8/PH/2021. This type of research was a laboratory experiment with a post-test-only control group design. The study population consisted of male Wistar (Rattus norvegicus) rats, 2–3 months old with a body weight of 150–200 grams, and healthy rats characterized by active movement responses and no defects. The number of samples used in this study were 24 male Wistar rats, which were then extracted and divided into two groups: the control group (K), which was given aquadest, and the treatment group (P), which was given purple leaves extract. Each group was further divided into three subgroups regarding the day of observation, namely the 3rd, 5th, and 7th day, each of which consisted of four rats.[15–17]

Identification of purple leaves was conducted in plants at the Jember State Polytechnic Plant Laboratory with letter number 118/PL17.8/PH/2021. Purple leaves extract is created by the maceration method. The purple leaves are washed, cut into small pieces, and dried by placing them at room temperature. The purple leaves were then dried in an oven at 50°C for 24 hours. Subsequently, the dried purple leaves were mashed into a powder using a blender. The powder was then macerated using 96% ethanol for three days, stirred every 24 hours, and filtered using filter paper. After that, the solution was concentrated in a rotary evaporator at 50°C to obtain a thick purple leaves extract. The extract was then diluted using aquadest so that it became purple leaves extract with a 10% concentration.[15,16]

Tooth extraction was performed on the left mandibular first molar. The extract and aquadest were given as much as 1.5 mL once a day orally using a gastric probe, then the animal was sacrificed, and the left mandible was taken. The rat jaws were then fixed with formalin buffer solution and decalcified using 10% formic acid solution for fourteen days with daily vibration. The soft tissue was cut mesiodistally, and histological preparations were made with Hematoxylin Eosin (HE) staining. Observation and calculation of the number of fibroblasts and blood vessels were carried out using a light microscope with 400x magnification in three fields of view. Then, the data were analyzed using the one-way ANOVA test. To assess the significant differences in each group, the Least Significant Difference (LSD) double comparison test was administered.[17–20]

RESULTS

The results showed in Figure 1, the formation of spindle-shaped cell fibroblasts with pink cytoplasm, dark purple cell

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nuclei, and cytoplasmic projections with tapered ends. The lumen of the visible blood vessel formation, which is oval in shape, is lined by a cell wall made of endothelial cells that are consistently placed around it (Figure 1). Based on the study results, on the 3rd, 5th, and 7th days, there were more fibroblasts and blood vessels in the treatment group that received 10% purple leaves extract compared to the control group that received aquadest (Table 1).

DISCUSSION

This study aimed to analyze the role of purple leaves extract (*Graptophyllum pictum (L.) Griff*) on the increase in the number of fibroblasts and blood vessels in the post-extraction socket of Wistar rats. Wistar rats were used in this study for their several advantages: They are as cheap, easy to obtain, maintain, and breed, and have a physiological

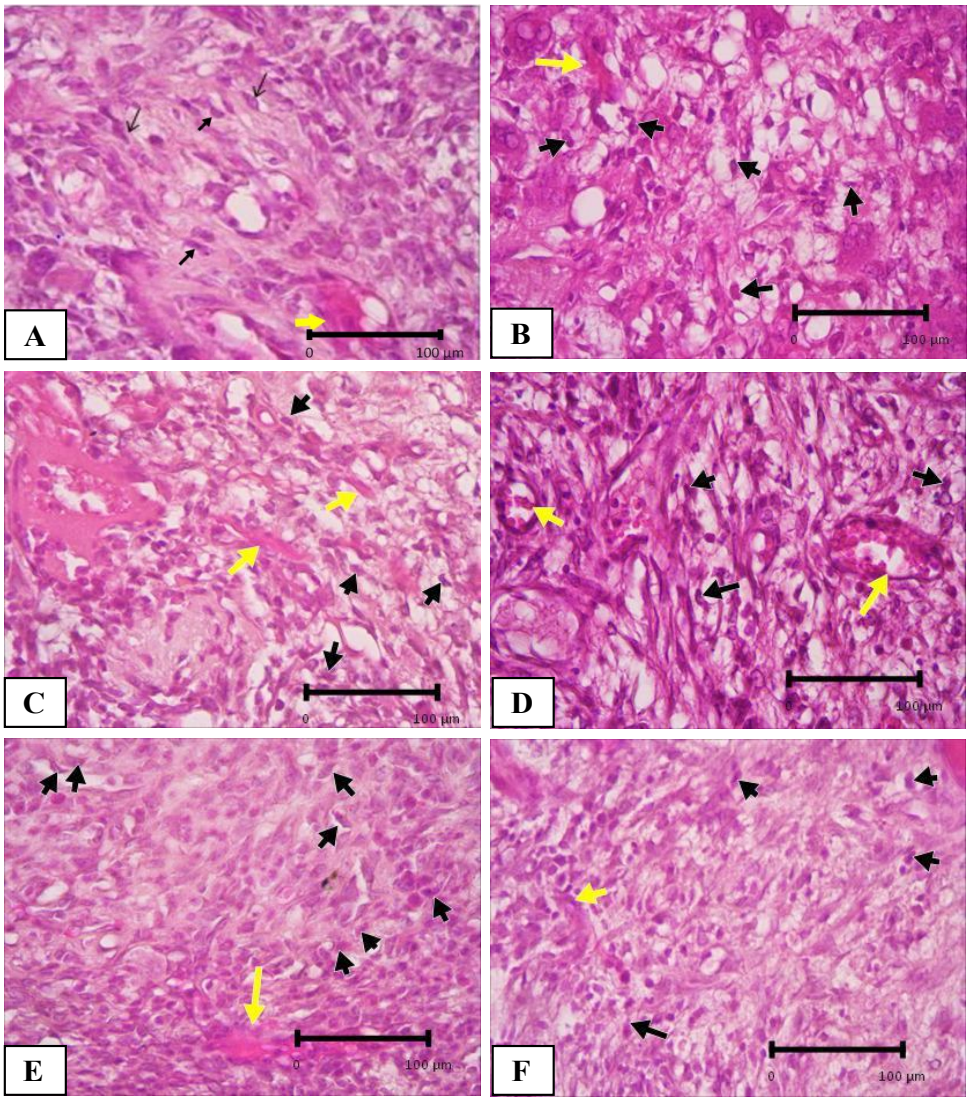

Figure 1. Histology of fibroblasts (black arrows) and blood vessels (yellow arrows) with HE staining at 400X magnification, scale bar 100µm. (A) Control group 3rd day, (B) Treatment group 3rd day, (C) Control group 5th day, (D) Treatment group 5th day, (E) Control group 7th day, and (F) Treatment group 7th day.

Table 1. The number of fibroblasts and blood vessels after the treatment with purple leaves extract

Sample Group	Fibroblasts (Mean± SD)		Blood vessels (Mean± SD)	
	Control	Purple Leaves Extract	Control	Purple Leaves Extract
3rd day	31.58 ± 0.16	33.08 ± 0.28*	4.08 ± 0.69	6.08 ± 0.74*
5th day	34.08 ± 0.54	41.83 ± 0.21*	6.75 ± 1.13	10.10 ± 1.56*
7th day	42.66 ± 0.49	50.08 ± 0.43*	11.25 ± 1.03	11.25 ± 1.23*

*Significant difference ($p<0.05$) between the control and treatment groups within the same day.

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system that is similar to humans.[18–20] Mesiodistal cutting direction in the preparation aimed to maintain the lateral wall and the apical part of the socket due to the healing process of the wound starting from the lateral wall and the apical part of the tooth socket.[18,19]

In the preparation of the purple leaves extract, 96% ethanol solvent was chosen, meaning that the 96% concentration of purple leaves extract was a mixture of two solvents: ethanol and water, with 96% ethanol and 4% water (v/v), so that it would effectively produce bioactive compounds in optimal amounts. The solvents were used to attract the active components of herbal medicines.[15,16] Purple leaves have alkaloids, flavonoids, steroids, saponins, and tannins. The compounds contained therein could be withdrawn through the extraction process and were strongly influenced by the presence of the solvent. For example, flavonoids could easily dissolve in polar solvents such as ethanol, butane, and acetone. Tannins cannot be dissolved in polar or non-polar solvents but are easily soluble in water, acetone, and alcohol. Several solvents, such as water, ethanol, methanol, acetonitrile, diethyl ether, and acetone, could be used in the extraction process. Ethanol was chosen as a solvent in this study because it has high solubility and can prevent the growth of fungi and bacteria to minimize contamination in the extract.[14–16]

The results showed that the number of fibroblasts and new blood vessels began to appear on the third day. Compared to the following days, the third day had the least number of fibroblasts and blood vessels. Because the new proliferative phase started on the third day after extraction and fibroblasts began to infiltrate the socket area due to several growth factors, such as PDGF and TGF-β, the number of fibroblasts and blood vessels increased on the 5th day and reached its peak on the 7th day.[4,9,19] In addition, on the third day, blood vessel buds formed as a site for the entry of endothelial progenitor cells into the blood circulation, where these endothelial cells could develop into mature endothelium and start the angiogenesis process.[4] The proliferation peak of fibroblasts, collagen fiber density, and cell endothelium was on the 7th day; the number of blood vessels and fibroblasts was maximal.[4,19,20] This is in accordance with Sari et al.'s [4] study, where on the 7th day, the expression of bFGF and the number of new blood vessels increased significantly.

The important mechanism of increasing purple leaves extract in the number of fibroblasts and blood vessels was related to its role in anti-inflammatory activity. The anti-inflammatory activities of this compound were through inhibiting the enzyme phospholipase A2, cyclooxygenase, and lipoxygenase. Inhibition of these enzymes was able to prevent the migration of inflammatory cells. By preventing the migration of inflammatory cells, it could inhibit the release of proinflammatory cytokines, namely IL-1, IL-6, TNF-α, and IFN-γ. [21,22] t On the contrary, it could increase the release of anti-inflammatory cytokines such as TGF-β,[21–24] which have the potential to stimulate the expression of epidermal growth factor (EGF), bFGF, PDGF, and VEGF, which play a role in inducing epithelial cells and fibroblasts and increasing migration and proliferation of endothelial cells, thereby stimulating the growth of new blood vessels. The formation of fibroblasts affects the formation of new connective tissue and provides strength to produce a good healing process.[7,25–27]

Giving 10% purple leaves extract to the treatment group on the 3rd, 5^{th,} and 7th days showed the number of fibroblasts and blood vessels was significantly higher than the control group. It was suspected through the mechanism that quercetin was known to be a flavonoid compound identified in purple leaves extract, where quercetin could bind to the TLR2 receptor on the surface of macrophages.[21] This binding was via the ERK 1/2 and JNK signaling pathways that were members of the MAPK4 superfamily. Through this signaling pathway, macrophages could activate the transcription factor NFkB to decrease the secretion of proinflammatory cytokines such as TNF-α and IFN-γ[22,24] and increase the secretion of anti-inflammatory cytokines such as TGF-β. The release of growth factors such as TGF-β have pro-angiogenic effects on endothelial cells.[25,26,28,29] This release occurs in response to inflammation induced by injury and accumulation of hypoxia-inducible factor-1a (HIF-1a) to hypoxia.[30,31] Under these hypoxic conditions, endothelial cells will trigger bFGF, resulting in microvascular growth. bFGF will then begin to produce mature endothelial cells to further synthesize new blood vessels.[4,30–32] Fibroblast growth factor and VEGF then bind to receptors on the cell surface equipped with tyrosine kinase activity. Activation of receptor kinases allows the incorporation of signal transduction pathways that regulate endothelial cell proliferation, migration, and differentiation. This increased secretion of anti-inflammatory cytokines can also trigger the proliferation of growth factor VEGF, which will initiate the growth of new blood vessels. [25,26,28]

Increasing the number of blood vessels will have an impact on the wound recovery process that takes place in the tooth socket after the extraction.[4,29,32] New blood vessels play an important role in the recovery process by removing waste and supplying nutrients and oxygen for metabolic processes during the healing process. A growth substance called VEGF initiates the growth of new blood vessels. During this procedure, the associated capillaries grow and eventually form a permanent network of blood vessels in the damaged tissue. The addition of new blood vessels was one of the factors that determined the success or failure of the wound recovery process. Increasing vascular permeability increased endothelial cell proliferation, endothelial cell mitosis, controlled endothelial cell migration, created new blood vessel lumens and macrophage chemotaxis, and vasodilation, all of which are goals of new blood vessel development.[33,34]

The increase in the number of blood vessels and fibroblasts occurred due to the synergistic effect of the active compounds in the purple leaves extract. It was known that purple leaves extract contains active compounds such as alkaloids, flavonoids, saponins, and tannins.[14,31]

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Saponin compounds could regulate VEGF, which could increase endothelial cell activity, thereby increasing the angiogenesis process. Saponins can also reduce the length of the inflammatory phase and secrete TGF-α, which can affect the differentiation of osteoblast cells.[33,35] Alkaloid compounds can play a role in preventing bacterial growth and protecting wounds from free radicals. Meanwhile, tannin compounds could also have the effect of reducing inflammation and preventing bacterial infections.[31,36,37]

In conclusion, after tooth extraction, male sockets of Wistar rat teeth can develop more fibroblasts and blood vessels when treated with purple leaves extract (*Graptophyllum pictum (L.) Griff*). Further studies that examine the growth factor PDGF, bFGF, and VEGF are urgently needed to explain the important role of purple leaves extract in wound healing, especially the proliferation and differentiation of cells into fibroblast and blood vessels.

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