

Potential Nano Gel Extract of Avocute Fruit (*Persea Americana Mill*) as Alternative in Prevention of Inflammation in White Rats White Rats Post-Extraction Wounds

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Abstract. Complications after tooth extraction include inflammation, bleeding, edema, discomfort, and dry socket. Both nonsteroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory drugs are used to treat inflammation. Using chemo drugs is not without side effects. Avocado seed is an herbal substance that is needed as an alternative therapy to reduce wound inflammation caused by tooth extraction. To prove the potential of nano gel (avocado seed extract) and can be applied as an alternative to prevent inflammation in wounds after tooth extraction of white rats. True experiment with randomized posttest with control group design. Consisting of intervention group nano gel avocado seed extract 10%, positive control group povidone iodine 10% and aquadest. Observations were made for 7 days. The variables studied were inflammation of the wound after tooth extraction of rats and histopathological examination (Lymphocytes, Neocapillary and Fibroblasts). According to the unpaired test results, there was no significant difference between the avocado and povidone groups ($p=0.143$), a significant difference between the avocado and aquadest groups ($p=0.001$), and a significant difference between the povidone and aquadest groups ($p=0.001$). $p = 0.015$). Application of avocado seed extract nanogels at concentrations of 10% and 10% povidone-iodine showed the same ability during wound regeneration and new blood vessel enlargement, and also reduced the number of lymphocyte inflammatory cells, as shown by histology Check confirmed. The administration of nano gel of avocado seed extract is effective and can be applied as an alternative to prevent inflammation in wounds after tooth extraction in white rats.

Keywords: Nano gel avocado seed extract, wound inflammation extraction, White Rats

INTRODUCTION

Dental and oral health is one part of body health that cannot be separated from each other, because dental and oral health can affect the health of the body as a whole (Laily et al., 2021). The presence of dental and oral diseases can affect health in general, although it does not cause death directly. Dental & oral health is generally not a priority for some people, and in fact teeth and mouth are the gateway for germs or bacteria to enter as a result can damage the health of other body organs (Hasiru et al., 2019).

From the 2018 Basic Health Research data, the proportion of dental & oral health problems and getting services from medical personnel in Indonesia is 57.6%, and the tooth extraction rate in Indonesia reaches 7.9%. Meanwhile, the tooth extraction rate in Central Java in 2018 reached 5.2% (Widya Paramita Lokapirnasari, 2017).

Tooth extraction is the process of removing the tooth from the alveolus, where the tooth can no longer be treated and can no longer be maintained. In tooth extraction, complications can occur due to local or systemic factors of the patient and can occur during or after the procedure. The action is taken (Winiswara et al., 2021). Complications due to post-extraction wounds are often found classified as intraoperative, after extraction and long after extraction. Bleeding, swelling, pain, dry socket, fracture, and mandibular dislocation are the most common complications of tooth extraction.

After tooth extraction can not be

separated from the formation of a wound or a hole called a socket. The basic response to damage or injury after tooth extraction is inflammation, which then proceeds in the process of tissue repair, namely the replacement of dead cells with living cells from fibrous tissue. The main cells involved in the wound healing process are fibrous. When tissue becomes inflamed, fibroblasts immediately migrate to the wound area, multiply and produce a collagen matrix to repair damaged tissue.

In general, the management of the inflammatory response is divided into two, including the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and steroid anti-inflammatory drugs. However, every use of chemical-based drugs must have side effects, ranging from a typical symptomatic response to the administration of salicylate NSAIDs, potential systemic toxicity, and teratogenic effects. Along with the increasing need for alternative treatments that are safe, effective, selective, economical, and have the same uses as chemical drugs, people have begun to turn to herbal medicine. WHO also recommends the use of traditional medicines including herbs in the maintenance of public health, prevention and treatment of disease (Organization, 2015).

Currently, research using herbal ingredients is the focus of researchers. *C. Avocado* plant (*Persea americana* mill) is one of the most widespread plants in Indonesia. This study used avocado seeds (*Persea americana* mill) as an alternative treatment to prevent inflammation in wounds after tooth extraction. Avocado

seeds contain several polyphenols that play a role in the process of preventing inflammation in wounds, including flavonoids, alkaloids, tannins, and saponins (Amelia et al., 2017).

Research conducted by Asep, et al. The effectiveness test of avocado leaf extract with a concentration of 5% w/w showed the best effectiveness on wound healing after 5 days. (8) Research conducted by Sastya, et al. The effectiveness of banana tree sap extract (*Musa paradisiaca*) whose content or compounds are the same as avocado seeds is effective and optimal in the process of accelerating the healing of socket wounds after tooth extraction (Khairunnisa et al., 2018). Research conducted by Mulia, et al. The effect of avocado seed extract (*Persea Americana* mill) on bleeding time in cutting the tail of mice (Strain Balb-c) has an effect on the acceleration of bleeding time, compared to negative controls (Winiswara et al., 2021).

Based on the above background, this study was conducted to prove the potential of avocado seed extract nano gel as an effort to prevent inflammation in wounds after tooth extraction and has great effectiveness as anti-inflammatory, antibacterial, antioxidant and antimicrobial.

MATERIALS AND METHODS

The type of research used is laboratory and field experiments, pure experiments with randomized posttest design with control group design. True experiment research with randomized posttest with control group design can be described as follows: 76

K1	C1	O1	
R	K2	C2	
	K3	X1	O3

Information:

R : Randomization

K1 and K2 : Control group

K3 : Intervention group

C1 : The negative control group was given aquades

C2 : Positive control group given 10% povidone iodine

X1 : The intervention group was administering 10% avocado seed extract nano gel

O1 : Posttest of giving aquades

O2 : Posttest administration of 10% povidone iodine

O3 : Posttest administration of 10% avocado seed extract nano gel

D. Research Subject

The research subjects were white wistar rats which were divided into 2 intervention groups and 1 treatment group, each group consisted of 9 rats. The 3 groups were divided into K1 as the 10% concentration of avocado seed extract nano gel treatment group, K2 as the positive control group (10% povidone iodine), K3 as the negative control group (aquadest).

Sample

The sample is part of the population that has been studied and is considered to represent the entire population. Determination of the sample size according to the Federer formula, the sample

determination formula for the experimental test is as follows⁷⁷:

$$(n-1) (t-1) 15$$

Information:

t is the number or number of groups given and n is the number of samples for each group used. In this study using 5 groups, namely 2 control groups and 3 treatment groups, so the calculation is as follows⁷⁷:

$$(n-1) (t-1) 15$$

$$(n-1) (3-1) 15$$

$$(n-1) (3-1) 15$$

$$(2) (n-1) 15$$

$$(2)n \geq 15 + 2$$

$$2n \geq 17$$

$$n \geq 17 : 2 = 9$$

The number of subjects in this study was 9, because the number of groups was 3, the total number of samples was 27 samples. Anticipating a drop out of a sample of 10% of the calculated sample. The calculation of the correction of the sample size that experienced dropout is as follows:

$$n = n / 1 - f$$

description:

n = number of samples

f = approximate proportion of dropout

$$n = n / 1 - f$$

$$= 9 / 1 - 0.1$$

$$= 9 / 0.9$$

$$= 10$$

Based on the above calculation, the sample required for each group is 10 rats.

The research group consisted of 3 treatment groups and 1 control group. So the total sample required is $10 \times 3 = 30$ samples. However, only 24 samples will be observed with the reason that 6 other samples were sacrificed for histopathological examination on days 3, 5 and 7.

The sampling method in this research is based on the inclusion and exclusion criteria that have been set by the researcher.

a. Inclusion criteria

1) The sample uses a type of white rat (*Rattus norvegicus wistar*)

2) Male gender

3) Weight between 180-250 grams

4) Age about 2-3 months (adult)

b. Exclusion Criteria

1) There are abnormalities seen in mice in the form of abnormalities in teeth.

2) Rats that die during the adaptation period

RESULTS AND DISCUSSION

Results

A. General description

This research was carried out after obtaining a research permit and the issuance of ethical clearance from Poltekkes Kemenkes Semarang. Research has been carried out in mid-May, namely making avocado seed extract nano gels at the Bionano Technology Laboratory UNDIP, Treatment of rats in the experimental animal lab of the Faculty of Medicine UNDIP, making histopathological

preparations at the Laboratory of Histology Preparation UNDIP, then for reading the results of preparations at the National Hospital. Diponegoro (K. Laboratory Installation).

This study describes the effectiveness of nano gel of avocado seed extract (*Persea Americana* mill) in accelerating the reduction of inflammation in wounds after tooth extraction in mice. The trial was carried out for 7 days. Reduction of inflammation in test animals was seen from the condition of the wound after tooth extraction according to a predetermined score, namely score 4 was severe inflammation, positive bleeding (not yet healed), score 3 was severe inflammation, positive bleeding, score 2 was moderate inflammation, negative bleeding, score 1 was mild inflammation, negative bleeding and a score of 0 is negative inflammation (cured). Then these results were proven by histopathological examination on days 3, 5 and 7.

B. Serving Data Analysis Description

Table 9. Results of Observation of Inflammation in Wounds After Teeth Extraction of Rats on K1 Nano Gel Avocado Seed Extract Day

to-	Intervention Group (K1)				
	K1	K2	K3	K4	K5
1	4	4	4	4	4
	4	4	4	4	4
2	3	3	3	3	3
	2	2	3	3	3
3	2	2	2	2	1
	2	2	2	2	2
4	1	2	1	1	1

	1	1	-	1	2
5	1	1	1	1	1
	1	1	-	1	1
6	0	0	0	1	0
	0	0	-	-	1
7	0	0	0	0	0
	0	0	-	-	0

The table above shows that the intervention group treated with the application of 10% avocado seed extract nano gel on the 3rd day of observation there was a score of 2 (moderate inflammation), On the 5th day of observation there was a score of 1 which means (mild inflammation) and on the 7th day Observation shows a score of 0 which means the wound has no inflammation.

Table 10. Results of Observation of Inflammation in Wounds After Rat Teeth Extraction at C+ (Povidone iodine 10%)

to-	Control Group +				
	C+ 1	C+2	C+3	C+4	C+5
	C+6	C+7	C+8	C+9	C+10
1	4	4	4	4	4
	4	4	4	4	4
2	3	4	4	3	4
	3	3	3	3	4
3	3	3	3	3	3
	3	2	3	3	3
4	2	3	3	3	3
	2	2	-	2	3
5	1	2	2	3	2
	1	1	-	2	2
6	1	1	1	2	1
	1	1	-	-	1
7	0	0	1	1	0

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0	0	-	-	0
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The table above shows that the C+ positive control group with 10% Povidone iodine application treatment on the 3rd day of observation there was a score of 3 (severe inflammation) meaning there was positive bleeding, on the 5th day of observation there was a score of 2 which means (moderate inflammation) and on the fifth day of observation there was a score of 2 (moderate inflammation). 7 observations showed a score of 0 which means the wound has no inflammation.

Table 11. Results of Observation of Inflammation in Wounds After Rat Teeth Extraction at C- (Aquadest) Day

to-	Control Group -				
	C-1	C-2	C-3	C-4	C-5
	C-6	C-7	C-8	C-9	C-10
1	4	4	4	4	4
	4	4	4	4	4
2	4	4	3	4	3
	3	4	4	4	4
3	4	3	3	4	3
	3	3	3	3	4
4	3	3	3	3	3
	3	3	-	3	3
5	2	3	2	3	2
	2	3	-	3	3
6	2	2	1	2	2
	2	2	-	-	2
7	1	1	0	1	1
	1	1	-	-	1

The table above shows that the C-negative control group with Aquadest application treatment on the 3rd day of observation there was a score of 4 (severe

inflammation) meaning there was positive bleeding, on the 5th day of observation there was a score of 3 which means (severe inflammation) and on the 7th day of observation shows a score of 1 which means the wound still has mild inflammation.

Table 12. Observation Results of the Presence of Lymphocyte Inflammatory Cells in Wounds After Rat Tooth Extraction

Field of view	K1 3	K1 5	K1 7	C+ 3	
	C+ 5	C+ 7	C-3	C- 5	C- 7
I	+2	+1	+2	+1	+1
	+2	+3	+2	+4	
II	+2	+2	+1	+1	+1
	+1	+2	+3	+2	
III	+1	+1	+1	+1	+1
	+1	+2	+3	+3	

Table 13. Observations of New Blood Vessels (Neocapillaryization) in Wounds Post Tooth Extraction in Rats

Field of view	K1 3	K1 5	K1 7	C- 3	
	C- 5	C- 7	C+3	C+ 5	C+ 7
I	1	1	1	2	1
	2	1	0	1	
II	1	0	0	2	1
	2	1	1	1	
III	1	1	0	1	2
	1	0	1	1	

Table 14. Observation Results of Connective Tissue (Fibroblasts) in Wounds After Rat Tooth Extraction

Field of view	K1 3	K1 5	K1 7	C- 3	
	C- 5	C- 7	C+3	C+ 5	C+ 7
I	3	3	2	1	2
	1	3	2	2	

II	3	2	3	1	1
	1	3	2	2	
III	2	2	2	2	1
	2	2	2	3	

Tables 12,13 and 14 above show the final results of the observation of lymphocyte inflammatory cells, namely there is a difference in the decrease in the number of lymphocyte inflammatory cells in K1, C+ and C-, and there is an increase in neocapillaryization in K1, C+ and C and an increase in fibroblasts. on day 7, which means the fibroblasts are parallel to the wound surface.

C. Inferential Data Analysis Serving

1. Data Normality Test

Table 15. Data Normality Test Results

Treatment	Chi-Square
Sig.	
Nano avocado seed gel 10%	0.001
Povidone iodine10%	0.000
Aquadest	0.000

Based on the normality test of the data using the Chi-Square test, it was found that the 7th day data for all groups had an abnormal distribution (Chi-Square test $p < 0.05$) so that p was rejected and it can be concluded that the variable data did not spread following the normal distribution. so that the calculation of the data on the 7th day used the Mann-Whitney nonparametric statistical test.

2. Mann-Whitney Non-parametric Test

Table 16. Different test groups of Avocado Seeds and Povidone

Treatment	N	Mean ±SD	P-Value
Avocado Seeds	8	0.3750±0.494	0.143
Povidone	8		

Table 17. Different test groups of Avocado Seeds and Aquadest

Treatment	N	Mean ±SD	P-Value
Avocado Seeds	8	0.3750±0.494	0.001
Aquadest	8		

Table 18. Different test of Povidone and Aquadest . groups

Treatment	N	Mean ±SD	P-Value
Povidone	8	0.3750±0.494	0.015
Aquadest	8		

Based on the unpaired test, the prevention of increased inflammation in the wound after tooth extraction of *Rattus norvegicus* day 7 white rats could be observed:

- The group that was given nano gel of avocado seed extract (*Persea americana* mill) in preventing increased inflammation after tooth extraction had the same ability as the group given 10% povidone iodine with p value = 0.143.
- The group that was given nano gel of avocado seed extract (*Persea americana* mill) in preventing an increase in inflammation after tooth extraction had a significant difference with the group given aquadest with p value = 0.001.
- The group that was given 10% povidone iodine in preventing the increase in inflammation after tooth extraction had

a significant difference with the group given aquadest with p value = 0.015.

Discussion

A. Nano Gel Avocado Seed Extract in Preventing Inflammation in Wounds After Teeth Extraction of White Rats

Inflammation of the wound is a complex process due to continuous biocellular and biochemical activities. The combination of vascular response, cellular activity, and the formation of chemical compounds as mediator substances in the wound area are interrelated components. When an injury occurs, the body has a mechanism to restore damaged tissue components by forming new and functional structures.⁸⁸ Several studies have shown that avocado seed extract can improve the prevention process and can also reduce the high risk of inflammation in post-extraction wounds. Avocado seeds are known to contain polyphenolic compounds, flavonoids, which are good in helping the process of preventing wound inflammation after tooth extraction. Flavonoids have biological and pharmacological activities, including anti-inflammatory and protecting blood vessels. The use of flavonoids in the health sector has been widely used in the treatment of inflammatory diseases.

The purpose of this study to observe the process of preventing inflammation in wounds after tooth extraction of white rats can be answered by the tables 9, 10 and 11. Wounds after tooth extraction of rats in the positive control group (C+) can recover completely from inflammation on day 7 and After tooth extraction, mice and the intervention group (K1) were able to recover completely from inflammation on

day 6. These results can also confirm that the hypothesis in this study is acceptable, namely that there are differences in the process of preventing wound inflammation after tooth extraction in the control group. positive and intervention groups.

Some of the advantages of nanoparticles is the ability to penetrate the intercellular spaces that can be penetrated by colloidal particles. In addition, nanoparticles are flexible to be combined with various other technologies. This capability opens wide potential to be developed for various purposes and targets. Another advantage is the increased affinity of the system due to an increase in the contact surface area by the same amount. In addition, nanoparticles also aim to overcome the solubility of poorly soluble active substances, improve poor bioavailability, modify drug delivery systems so that drugs can go directly to specific areas. In this study, the Particle Size Analyzer (PSA) test was used to measure the particle size distribution using the Dynamic Light Scattering (DLS) method using the Non-Invasive Back Scatter (NIBS) technique. which is 151.8 nm (nanometer), in the results it is included in the nano size requirement because the nanoparticle size ranges from (10-1000 nm). With a touch of nano technology, it is hoped that the active substances will be able to penetrate cell walls. In the provision and use of avocado seed extract nano gel which synergizes the wound healing effect and anti-inflammatory effect of avocado seed extract nano gel will provide a better inflammation prevention effect and change pharmacogenetic properties and its pharmacogenomics to be faster.⁷³ These

results are included in the nano size requirements because the nanoparticle size ranges from (10-1000 nm). With a touch of nano technology, it is hoped that the active substances will be able to penetrate cell walls. In the provision and use of avocado seed extract nano gel which synergizes the wound healing effect and anti-inflammatory effect of avocado seed extract nano gel will provide a better inflammation prevention effect and change pharmacogenetic properties and its pharmacogenomics to be faster.⁷³ These results are included in the nano size requirements because the nanoparticle size ranges from (10-1000 nm). With a touch of nano technology, it is hoped that the active substances will be able to penetrate cell walls. In the provision and use of avocado seed extract nano gel which synergizes the wound healing effect and anti-inflammatory effect of avocado seed extract nano gel will provide a better inflammation prevention effect and change pharmacogenetic properties and its pharmacogenomics to be faster (Marhamah et al., 2014).

Lymphocytes are cells that play a role in the immune system. The number of lymphocytes increases in inflammation, because lymphocytes migrate to the wound area on day 1, then the number will peak on days 3 to 6, and on the seventh day the lymphocytes decrease. Observations of lymphocyte inflammatory cells in the 10% avocado seed extract nano gel group (*Persea Americana* mill) obtained on the 3rd day were less than 50 cells per field of view, then continued to decrease on the 5th and 7th days, which may be due to the acute inflammatory process occurring

more rapidly so that on day 1 the lymphocytes which are inflammatory cells infiltrate the wound area more rapidly. On the 3rd, 5th, and 7th days the number of lymphocytes decreased, indicating that the antigen was no longer there, the inflammatory phase was over.

The most important component in the tissue healing process is the rearrangement of the collagen network which can affect the quality of the wound. The targets in the body's biological process of compensating wounds are components that play a role in the stages of wound healing. Fibroblasts are one of the components of wound healing in the form of cells that are widely distributed in connective tissue, producing collagen precursor substances, elastic fibers, and reticular fibers. In the wound healing stage, fibroblasts play an important role in the process of fibroplasia. Fibroplasia is a wound repair process that involves connective tissue which has four components, namely the formation of new blood vessels, migration and proliferation of fibroblasts, deposition of ECM (extracellular matrix), and maturation and organization of fibrous tissue (remodelling). In these four components, Fibroblasts play a role in the fibrosis process involving two of the above components, namely fibroblast migration and proliferation and ECM deposition by fibroblasts. already parallel to the wound surface and has a thickness of tissue (fibroblasts), in the intervention group the administration of nano gel of avocado seed extract was better because of the flavonoid content in the avocado seed which functions as an anti-inflammatory so that it can increase the wound inflammation

process after tooth extraction. In the negative control that was only given feed and aquades, this was because it did not contain anything, so that the wound healing process after tooth extraction continues even though it takes a long time, because of the inflammatory phase from within the body to the wound. This happens because there are still microbes and tissue damage that must be phagocytized by cells in the wound area, which are still much different from the active ingredients in the avocado seed extract nano gel.

And the neocapillary observation showed that the final result on day 7 was a decrease in neocapillary formation because the wound had started to heal so it had started to stop the neocapillary formation process. This decrease indicates that the neocapillaries formed on days 3 and 5 are considered sufficient to perform the task as a blood supply containing nutrients and other factors that are useful for healing so that the wound begins to close. The results showed that the average number of neocapillaries in the treatment group was higher than the negative control group. The results also showed that distilled water did not have active ingredients so that the wound healing process took longer and had a low number of neocapillaries.

The use of herbal plants as an alternative in reducing inflammation has been carried out in several studies, but no one has researched on nano gel which is a novelty or latest innovation in this study. Research by Yani Corvianindya Rahayu used avocado seed powder with a concentration of 10% (*Persea Americana* mill) to reduce the number of PMN neutrophils in mice

induced by E.Coli, and on the third day there was a change and affect the number of PMN neutrophils.⁹¹ Another study used banana tree sap extract. (*Musa paradisiaca*) on the healing of socket wounds after tooth extraction and the results showed that there was a reduction in the level of inflammation and bleeding from day 1 to day 7 during administration of banana tree sap ethanol extract. Then for other studies using snakehead fish (*Channa striata*) chitosan nanoparticles for wound healing after tooth extraction and showed the results that the activity of chitosan nanoparticle albumin snakehead fish extract on wound healing was faster than that without treatment, where the chitosan nanoparticle preparation was given snakehead fish extract on day 14 was completely covered by granulation tissue.⁹² In this study, the wound after tooth extraction of white rats on day 6 in the avocado seed extract nano gel group had no inflammation and in the avocado seed extract nano gel group there was no inflammation. inflammation is faster than 10% povidone iodine and aquades. Not all herbal plants have the ability to stimulate fibronilysis in wounds, Therefore nano gel avocado seed extract can prevent inflammation faster than some of the herbal plants above. One theory states that the process of preventing inflammation in post-tooth extraction wounds occurs due to fibroblast activity which can increase collagen tissue in wounds so that inflammation prevention of post-tooth extraction wounds in mice can occur which is influenced by the application of herbal ingredients, namely nano gel avocado seed extract.

Avocado seeds also have biological and pharmacological activities from polyphenolic compounds, namely flavonoids, including anti-inflammatory, antibacterial, antioxidant and protecting blood vessels. A journal review by Yani Corvianindya Rahayu mentioned the benefits of avocado seeds in reducing neutrophil PMN cells that cause inflammation in wounds after tooth extraction in mice induced by *E. Coli* bacteria. The results of this study are in line with the journal above, it is known that the application of nano gel of avocado seed extract has the same potential as 10% povidone iodine in preventing increased inflammation in post-extraction wounds with a p-value of 0.143. Nano gel of avocado seed extract can prevent inflammation in the wound after tooth extraction and the duration of inflammation is also shorter and can minimize the occurrence of infection or inflammation caused by the entry of microorganisms into the wound. Inflammation of post-extraction wounds is a common problem in the community and is recognized as a more common cause during treatment. This can be avoided by giving avocado seed extract nano gel but further research needs to be done in direct application to humans in order to avoid things that are not desirable.

CONCLUSIONS

The administration of nano gel of avocado seed extract (*Persea Americana* mill) with a concentration of 10% on the wound after tooth extraction of white rats (*Rattus norvegicus wistar*) has potential and

can be applied as an alternative herbal ingredient to prevent inflammation. The administration of nano gel of avocado seed extract (*Persea Americana* mill) at a concentration of 10% did not have a significant difference with the administration of 10% povidone iodine in preventing inflammation in post-tooth extraction wounds in rats. The administration of nano gel of avocado seed extract (*Persea americana* mill) with a concentration of 10% and povidone iodine 10%, has the same ability in the process of wound regeneration and increases new blood vessels and can also reduce the number of lymphocyte inflammatory cells as evidenced by histological examination.

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