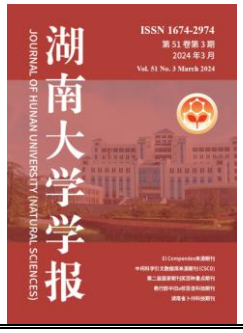

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Effect of Black Crab (*Scylla Serrata*) Chitosan Gel on the Three-Dimensional Socket Response and Fibroblasts after Tooth Extraction in *Rattus Norvegicus*

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Abstract: Tooth extraction is a common procedure in dentistry that can result in wounds to the soft and hard tissues of the alveolar process, thereby triggering the healing process. The wound healing process is often complicated by several factors, leading to delayed wound healing. The principles of wound healing involve four phases: hemostasis, inflammation, proliferation, and remodeling. This study aimed to determine the effect of black crab *(Scylla serrata)* chitosan gel on three-dimensional socket response and fibroblast proliferation after tooth extraction in Wistar rats *(Rattus norvegicus)*. In this study, chitosan material with a degree of deacetylation of 84.9% was used, thus exhibiting good biological properties in the wound healing process. This research is an experimental study with a post-test only with a controlled group design. The sampling technique used was purposive sampling, and the sample size was calculated using the Federer formula. Observations were made by measuring the mesial-distal, lingual-buccal, and socket depths using calipers and the UNC15 probe and observing the number of fibroblasts histologically on Days 1, 3, and 7. The results of the one-way ANOVA and post hoc LSD tests indicate significant outcomes in socket wound closure and fibroblast proliferation in the chitosan gel group. This study demonstrates that black crab *(Scylla serrata)* chitosan gel is effective in accelerating socket wound closure and stimulating fibroblasts in socket wounds after tooth extraction.

Keywords: tooth extraction, black crab chitosan gel, socket response, fibroblast.

锯缘青蟹壳聚糖凝胶对褐家鼠拔牙后三维窝反应及成纤维细胞的影响

摘要：拔牙是牙科中的常见手术，可能会导致牙槽突的软组织和硬组织受伤，从而引发愈合过程。伤口愈合过程往往因多种因素而变得复杂，导致伤口愈合延迟。伤口愈合的原理涉及四个阶段：止血、炎症、增殖和重塑。本研究旨在确定黑蟹（锯缘青蟹）壳聚糖凝胶对维斯塔大鼠（褐家鼠）拔牙后三维窝反应和成纤维细胞增殖的影响。本研究使用脱乙酰度为84.9%的壳聚糖材料，因此在伤口愈合过程中表现出良好的生物学特性。本研究是一项实验研究，仅进行受控组设计的后测。所采用的抽样技术是有目的抽样，样本量使用费德勒公式计算。通过使用卡尺和北卡罗来纳大学15探针测量近中-远中、舌-颊和牙槽深度并在第1、3和7天观察成纤维细胞的组织学数量来进行观察。单向方差分析和事后分析的结果迷幻剂测试表明壳聚糖凝胶组在牙槽窝伤口闭合和成纤维细胞增殖方面具有显着效果。这项研究

表明，黑蟹（锯缘青蟹）壳聚糖凝胶可有效加速牙槽窝伤口闭合并刺激拔牙后牙槽窝伤口中的成纤维细胞。

关键词：拔牙，黑蟹壳聚糖凝胶，牙槽反应，成纤维细胞。

1. Introduction

Tooth extraction is a common procedure in dentistry. The extraction results in wounds in soft and hard tissues of the alveolar process, causing injury. Often, this procedure can lead to complications that slow down the healing process [1]. The impacts of these complications may include pain, unpleasant odor, exudate discharge, and decreased patient productivity. Various factors contribute to delayed wound healing, including age, poor oral hygiene, smoking, and the size of the post-extraction wound [2].

The wound healing process involves the replacement of damaged or lost tissue with new tissue to restore function. The principles of wound healing encompass four phases: hemostasis, inflammation, proliferation, and remodeling. The initial response to the wound or damage begins with hemostasis, followed by tissue healing characterized by the replacement of cells with fibrous tissue. Fibroblast cells play a crucial role in the healing process. During the proliferation phase, these cells move to the wound area, multiply, and produce collagen matrix to repair the damaged tissue [3]. Optimal wound healing management has led to advancements in the understanding of wounds, healing, and their treatment. The use of natural substances for wound healing has gained acceptance due to the minimal side effects.

In Indonesia, solid waste, such as crab shells, amounts to approximately 1000 tons per year. This waste has been proven to contain chitin, which can be processed into chitosan [4]. Chitosan is a linear random copolymer of N-acetyl-D-glucosamine and deacetylated D-glucosamine linked by β-1,4 glycosidic bonds [5]. Chitosan is safe for use in healthcare, serving purposes such as wound healing, tissue regeneration, hemostatic material, wound dressing, and even capsule coatings [6]. Studies have shown that chitosan gel is an effective wound healing preparation because of its good hemostatic, biocompatible, and biodegradable properties, with no significant side effects [7]. Majid Ali [8] revealed that chitosan from black crab *(Scylla serrata)* shells has higher affinity and deacetylation degree (up to 87%) than other crab types, making it biologically superior.

Based on the above description, it is evident that there has been significant research on the use of chitosan in aiding wound healing. Therefore, the researchers investigated the effectiveness of using black crab *(Scylla serrata)* chitosan gel in healing after tooth extraction, considering the clinical three-dimensional socket response and the number of fibroblasts.

2. Materials and Methods

This research was conducted in the Pharmacology and Therapeutics Laboratory at the Faculty of Medicine, the Analytical Chemistry Laboratory at the Faculty of Mathematics and Natural Sciences, University of North Sumatera, and the Prospective Pathological Anatomy Laboratory. The population of this study consisted of Wistar rats, and the sample size was calculated using the Federer formula. The required number of samples was 30 Wistar rats. The samples were divided into six groups: (1) placebo gel CMC-Na on Day 1, (2) placebo gel CMC-Na on Day 3, (3) placebo gel CMC-Na on Day 7, (4) 3% chitosan gel on Day 1, (5) 3% chitosan gel on Day 3, and (6) 3% chitosan gel on Day 7. Each group consisted of five samples.

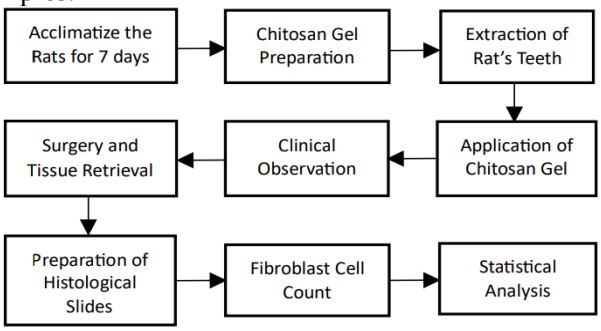

Fig. 1 Flowchart of the research methodology (The authors)

2.1. Chitosan Gel Preparation

The preparation of 3% chitosan gel was achieved by dissolving 3 g of chitosan powder in 100 ml of 1% acetic acid with a pH of approximately 4, following factory regulations. Once the chitosan is dissolved, stirring is conducted with a stirrer while adding NaOH to adjust the pH to a neutral range. Subsequently, 3% chitosan gel is transferred into 100-ml bottles.

Fig. 2 Preparation of the chitosan gel (The authors)

2.2. Extraction of Rat Teeth

Before the experiment, the rats were acclimatized for 7 days. Subsequently, body weight measurements were conducted before the rats received treatment. General anesthesia in the form of ketamine injection was administered at a dose adjusted to the weight of the experimental animals. Tooth extraction was performed by restraining the lower part of the rat, followed by an incision on the left lower incisor region using a scalpel and no. 15 blade. A curved artery clamp was placed on the tooth to be extracted, followed by gently rocking the tooth laterally until it was dislodged.

Fig. 3 Extraction of the experimental animal teeth (The authors)

2.3. Application of the Chitosan Gel

Chitosan gel is applied to the socket using a 1 cc syringe twice a day for 7 days. The use of chitosan gel in both the control and treatment groups begins immediately after the injury. Group I employs placebo gel, specifically CMC-Na, as a negative control, whereas Group II uses chitosan gel with a concentration of 3%, administered in a volume of 0.1 ml.

Fig. 4 Application of 3% chitosan gel (The authors)

2.4. Clinical Observation of the Socket Response in Three Dimensions

Clinical observation of the three-dimensional socket response in the experimental animals was conducted on Days 1, 3, and 7 after tooth extraction. The observation involved assessing changes in mesial-distal width, lingual-buccal width, and socket depth. These observations were measured using calipers.

Fig. 5 Measurement of the socket response (The authors)

2.5. Experimental Animal Surgery and Tissue Retrieval

The rats were euthanized by anesthetizing them using ketamine via an intraperitoneal technique. After the rats are deceased, excision is performed on the jaw tissues, which are then fixed with a Buffered Neutral Formalin (BFN) 10% solution and placed in a specialized storage container.

Fig. 6 Euthanasia and collection of rat jaw tissues (The authors)

2.6. Preparation of Histological Slides and Fibroblast Cell Count Observation

The extracted tissues were further decalcified by immersion in 10% EDTA solution. The fibroblast cell count in tissue preparations was assessed using a binocular microscope at 400x magnification, with an ocular graticule placed within the lens, divided into five fields to avoid repeated counting.

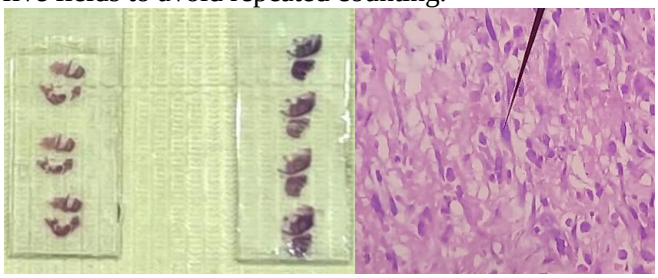

Fig. 7 Tissue preparation and histology of the fibroblasts (The authors)

3. Results

Data processing and analysis were performed using SPSS. The Shapiro-Wilk test was employed to assess the normality of the data. Subsequently, a one-way ANOVA test was performed to determine the effectiveness of chitosan gel from black crab shell *(Scylla serrata)* in tooth socket healing in vivo. This was followed by a post hoc LSD test to examine the comparisons between the three observation days.

3.1. Three-Dimensional Socket Closure Response after Tooth Extraction

The assessment of wound healing speed after tooth extraction in male Wistar rats was clinically evaluated using the residual socket volume (RSV) calculation method. In the control group, the average and standard deviation of the RSV for Wistar rat socket wounds treated with placebo gel (CMC-Na) on Days 1, 3, and 7 were 0.66 ± 0.11, 0.59 ± 0.11, and 0.48 ± 0.10, respectively. Meanwhile, in the treatment group, the

average and standard deviation of the RSV for Wistar rat socket wounds in the treatment group after applying 3% chitosan gel from the black crab shell *(Scylla serrata)* on Days 1, 3, and 7 were 0.51 ± 0.73, 0.44 ± 0.07, and 0.26 ± 0.04, respectively.

Table 1 One-way ANOVA test for the socket response (The authors)

Group	Day	Sample	Mean±SD	P-Value
CMC-Na	Day 1	4	0.66±0.11	0.000
	Day 3	4	0.59±0.11	
	Day 7	4	0.48±0.10	
3% Chitosan Gel	Day 1	4	0.51±0.73	0.000
	Day 3	4	0.44±0.07	
	Day 7	4	0.26±0.04	

Based on the results of the one-way ANOVA test, there was a significant difference in the 3% chitosan gel treatment group between observations on Days 1, 3, and 7, with a significance value of p=0.001 (p<0.05). Meanwhile, in the control group with a placebo of CMC-Na, there was no significant difference between observations on Days 1, 3, and 7, with a significance value of p=0.121 (p>0.05). According to the results of the post hoc LSD test, in the CMC-Na group, there was a significant difference between observations on Days 1 and 7 (p=0.048, p<0.05), but no significant difference was observed between observations on Days 1 and 3 (p=0.441, p>0.05) and between Days 3 and 7 (p=0.172, p>0.05). In the 3% chitosan gel group, there was a significant difference between observations on Days 1 and 7 (p=0.000, p<0.05) and between Days 3 and 7 (p=0.004, p<0.05). However, no significant difference was observed between observations on Days 1 and 3 (p=0.158, p>0.05).

Table 2 Post hoc LSD test of the socket response (The authors)

Group	Day		P-Value
CMC-Na	Day 1	Day 3	0.441
		Day 7	0.048*
	Day 3	Day 7	0.172
3% Chitosan Gel	Day 1	Day 3	0.158
		Day 7	0.000*
	Day 3	Day 7	0.004*

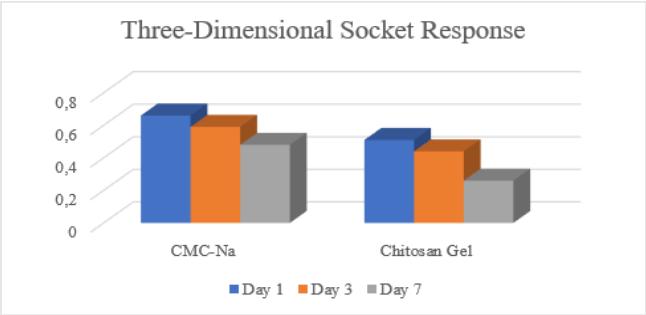

Fig. 8 RSVs on Days 1, 3, and 7 (The authors)

3.2. Number of Fibroblasts in Healing Socket Wounds after Tooth Extraction

In the control group, the average and standard deviation of the number of fibroblasts from the sockets of Wistar rats treated with placebo gel (CMC-Na) on days 1, 3, and 7 were 38.85 ± 4.90, 47.30 ± 1.20, and 75.50 ± 7.78, respectively. Meanwhile, in the treatment group, the average and standard deviation of the number of fibroblasts from the sockets of Wistar rats in the treatment group after applying 3% chitosan gel from the black crab shell *(Scylla serrata)* on Days 1, 3, and 7 were 24.05 ± 0.91, 94.70 ± 24.40, and 129.85 ± 25.30.

Table 3 One-Way ANOVA test of fibroblast cell proliferation (The authors)

Group	Day	Sample	Mean±SD	P-Value
CMC-Na	Day 1	4	38.85±4.90	0.000
	Day 3	4	47.30±1.20	
	Day 7	4	75.50±7.78	
3% Chitosan Gel	Day 1	4	24.05±0.91	0.000
	Day 3	4	94.70±24.40	
	Day 7	4	129.85±25.30	

Based on the results of the one-way ANOVA test, there was a significant difference in fibroblast cell proliferation across all data groups between the 3% chitosan gel treatment group and the CMC-Na placebo control group on observations on Days 1, 3, and 7, with a significance value of p=0.000 (p<0.05). According to the pos hoc LSD test, in the CMC-Na group, there was a significant difference in the number of fibroblasts between observations on Days 1 and 7 and on Days 3 and 7, with a significance value of p=0.000 (p<0.05). However, there was no significant difference between observations on Days 1 and 3, with a significance value of p=0.053 (p>0.05). Meanwhile, in the 3% chitosan gel group, there was a significant difference between observations on Days 1 and 3 with a p-value of 0.001 (p<0.05), between Days 1 and 7 with a p-value of 0.000 (p<0.05), and between Days 3 and 7 with a p-value of 0.037 (p<0.05).

Table 4 Post hoc LSD for fibroblast cell proliferation (The authors)

Group	Day		P-Value
CMC-Na	Day 1	Day 3	0.053
		Day 7	0.000*
	Day 3	Day 7	0.000*
Chitosan Gel 3%	Day 1	Day 3	0.001*
		Day 7	0.000*
	Day 3	Day 7	0.037*

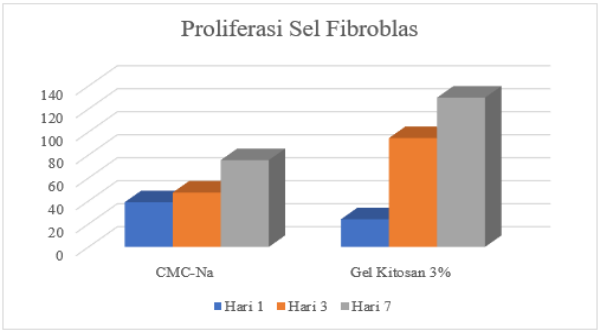

Fig. 9 Mean fibroblast cell count on Days 1, 3, and 7 (The authors)

4. Discussion

Healing post-tooth extraction wounds consists of

four phases: hemostasis, inflammation, proliferation, and remodeling or maturation. In the hemostasis phase, chitosan gel can shorten the bleeding time. In this study, the bleeding time after tooth extraction in the treatment group was shorter than that in the control group. This aligns with Chen et al.'s [9] research on the effectiveness of 78% deacetylated chitosan in blood clotting time, reporting that chitosan can form coagulation upon contact with blood. The hemostatic properties of chitosan come from its positive charge, which can initiate the aggregation of negatively charged erythrocytes [10]. Adhesion and aggregation of erythrocytes are the initial steps of chitosan in stopping bleeding. Chitosan can cause red blood cells to adhere, aggregate, and change shape, forming a strong blood clot that blocks the bleeding point. Chitosan has nonspecific membrane adhesion properties, allowing it to adhere to the wound area and interact with hemoglobin through hydrogen bonding, electrostatic interactions, and hydrophobic interactions, resulting in microstructural changes in hemoglobin and increased viscosity [11]. In addition, the amino groups on chitosan molecules can create a mesh-like spatial structure, enhancing interactions between blood components and chitosan, supporting the formation of a strong blood clot [10].

In the inflammation phase, chitosan plays a role in reducing inflammation signs by enhancing the functions of inflammatory cells such as polymorphonuclear (PMN) cells, macrophages, and fibroblasts. The N-acetyl-D-glucosamine monomer in chitosan binds to macrophage's main receptors, triggering migration and proliferation of macrophages, enhancing the phagocytosis process [12]. This leads to a rapid progression of the inflammation phase and a decrease in the signs of inflammation. This is consistent with de Jesus et al.'s [13] study, which showed that 3% chitosan hydrogel can reduce inflammation signs compared with the group without chitosan.

The post hoc LSD test results showed a nonsignificant difference in the mean residual socket volume between the 3% chitosan gel treatment group on Days 1 and 3, with a significance value of $p=0.158$ ($p>0.05$). However, significant differences were observed between Days 3 and 7 and between Days 1 and 7, with significance values of $p=0.004$ and $p=0.000$ ($p<0.05$). The non-significant difference in the RSV between Days 1 and 3 in the 3% chitosan gel group is related to the ongoing inflammation phase on Day 1, whereas the proliferation phase begins on Day 3, showing no significant differences in socket closure dimensions. The significant differences in the RSV between Days 3 and 7 and between Days 1 and 7 indicate that chitosan plays a crucial role in the proliferation phase. In this phase, chitosan amino groups stimulate fibroblast secretion. Stimulation begins when chitosan contacts the oral mucosa tissue, gradually depolymerizing polymer groups to release N-acetyl-β-D-glucosamine. This triggers GAGs secretion, accelerating the formation of GAGs-collagen bonds to promote granulation tissue formation and reepithelialization processes, leading to rapid wound closure [14]. This aligns with the findings of Hartono et al. [15], who demonstrated that chitosan gel enhances reepithelialization by stimulating the migration and proliferation of inflammatory cells.

In this study, aside from measuring residual socket volume, an indicator for evaluating the socket closure process is the number of fibroblast cells that proliferate. The one-way ANOVA test results showed a significant difference in the 3% chitosan gel treatment group and placebo CMC-Na gel control group, with respective significance values of 0.000 ($p<0.05$). The post hoc LSD test indicated a significant difference in the chitosan group's fibroblast cell count between Days 1 and 3, with a significance value of $p=0.001$ ($p<0.05$). The increase in the fibroblast cell count on Day 3 is due to fibroblast proliferation induction by growth factors produced by macrophages. Chitosan contains N-acetyl glucosamine monomers that trigger macrophage migration and proliferation, leading to increased metabolic activity, such as the secretion of VEGF, FGF, TGF, and angiopoietin, stimulating fibroblast cell proliferation [12]. This is consistent with Feng et al. [14], who stated that epithelial migration activity develops well on Day 3 and proliferating cells increase. In contrast, the placebo CMC-Na gel group showed no significant difference, with a significance value of $p=0.053$ ($p>0.05$), because CMC-Na gel does not contain compounds that stimulate fibroblast cell proliferation [16].

In this study, both the chitosan gel and CMC-Na gel groups showed significant differences between Days 3 and 7 and between Days 1 and 7 ($p<0.05$). However, the chitosan gel group exhibits higher fibroblast cell proliferation than the CMC-Na gel group because chitosan can support collagen formation, prevent scar tissue formation, and promote fibroblast cell formation [17]. This study's results indicate that 3% chitosan gel plays a role in accelerating socket wound closure after extraction in male Wistar rats. This aligns with Gupta et al.'s [18] research on the effectiveness of chitosan in accelerating wound healing after extraction.

5. Conclusion

The chitosan gel from black crab *(Scylla serrata)* is effective in accelerating wound closure and increasing the number of fibroblasts in the socket after tooth extraction as part of the wound healing process. The chitosan gel demonstrates faster wound closure than the control group, as observed on Days 3 and 7. In addition, the chitosan gel stimulated and enhanced fibroblast cell proliferation from the first day of application, reaching its peak on the 7th day, in contrast to the control group. This research indicates that black

crab chitosan gel *(Scylla serrata)* is suitable for use as an intervention in wound care, particularly for socket wounds after tooth extraction. Therefore, black crab chitosan gel as a new material for accelerating the post-tooth extraction healing process can serve as a basis for development in other fields of dentistry. Suggestions for further research include conducting studies using chitosan with different sizes and formulations. In addition, it is essential to investigate the effectiveness of black crab *(Scylla serrata)* chitosan on other cells involved in the wound healing process.

Acknowledgment

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