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ORIGINAL ARTICLE

CHITOSAN FROM BLACK SOLDIER FLY (*HERMETIA ILLUCENS*) PUPAE INCREASES OSTEOBLASTS AND DECREASES OSTEOCLASTS POST-TOOTH EXTRACTION: *IN VIVO* STUDY

Quitosano de pupas de la mosca soldado negra (*Hermetia illucens*) aumenta los osteoblastos y disminuye los osteoclastos después de la extracción dental: estudio *in vivo*

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ABSTRACT

Introduction: Tooth extraction can cause injury to the alveolar process in the form of an open socket. Black Soldier Fly (BSF) pupa contains 35% chitin which can be processed into chitosan through chitin deacetylation. Chitosan has high osteoinduction, easy application, and good biodegradability for bone regeneration. **Aim:** To evaluate the expression of osteoblast and osteoclast numbers following tooth extraction and the application of chitosan BSF pupa gel.

Material and Methods: Chitosan from BSF pupa was formulated into a gel. A total of 18 *Cavia cobaya* were anesthetized with an intramuscular injection in the upper thigh, using a combination of ketamine (50 mg/kg body weight) and xylazine (5 mg/kg body weight), divided into control group (n = 9) not given BSF chitosan gel in the post-tooth extraction socket and the treatment group (n = 9) given BSF chitosan pupa gel (0.3 ml) in the post-tooth extraction socket. Samples were decapitated on days 7, -14, and -21 to see the expression of the number of osteoblasts and osteoclasts. Data was analyzed using Oneway ANOVA.

Results: There was an increase in the number of osteoblasts in the treatment group on day 7 (52.20±1.90); day 14 (91.53±1.00); day 21 (104.13±5.33) of the control group day 7 (39.80±5.43); day 14 (61,13±1,10); day 21 (82,60±2.11). There was a decrease in the number of osteoclasts in the treatment group on day 7 (4.86±1.51); day 14 (9±0.34); day 21 (2.66±0.11); of the control group day 7 (9.83±0.35); day 14 (12.80±0.72); day 21 (2.46±0.11) (p=0.00 oneway test ANOVA).

Conclusions: The application of chitosan derived from BSF pupa has the potential to accelerate bone formation by increasing the number of osteoblasts and reducing the number of osteoclasts after tooth extraction, suggesting its beneficial role in bone regeneration.

Keywords: *Bone remodeling; Chitosan; Diptera; Pupa; Osteoblasts; Osteoclasts.*

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RESUMEN

Introducción: La extracción dental puede causar lesiones en el proceso alveolar, formando un alvéolo abierto. La pupa de la mosca soldado negra (BSF) contiene un 35 % de quitina, que puede transformarse en quitosano mediante su desacetilación. El quitosano presenta alta osteoinducción, es de fácil aplicación y presenta buena biodegradabilidad, para la regeneración ósea. **Objetivo:** Evaluar la expresión de osteoblastos y osteoclastos tras la extracción dental y la aplicación de gel de quitosano de pupa de BSF.

Material y Métodos: El quitosano de la pupa de BSF se formuló en un gel. Se anestesiaron 18 ejemplares de *Cavia cobaya* mediante inyección intramuscular en la parte superior del muslo, utilizando una combinación de ketamina (50 mg/kg de peso corporal) y xilazina (5 mg/kg de peso corporal). Se dividieron en un grupo control (n = 9), al que no se le administró gel de quitosano BSF en el alvéolo posterior a la extracción dental, y un grupo de tratamiento (n = 9), al que se le administró gel de pupa de quitosano BSF (0,3 ml) en el alvéolo posterior a la extracción dental. Las muestras se decapitaron los días 7, -14 y -21 para observar la expresión del número de osteoblastos y osteoclastos. Los datos se analizaron mediante ANOVA unidireccional.

Resultados: Se observó un aumento en el número de osteoblastos en el grupo de tratamiento el día 7 (52,20 ± 1,90); el día 14 (91,53 ± 1,00); Día 21 (104,13 ± 5,33) del grupo control, día 7 (39,80 ± 5,43); día 14 (61,13 ± 1,10); día 21 (82,60 ± 2,11). Se observó una disminución en el número de osteoclastos en el grupo de tratamiento en los días 7 (4,86 ± 1,51); día 14 (9 ± 0,34); día 21 (2,66 ± 0,11); del grupo control, día 7 (9,83 ± 0,35); día 14 (12,80 ± 0,72); día 21 (2,46 ± 0,11) (p= 0,00, prueba ANOVA unidireccional).

Conclusiones: La aplicación de quitosano derivado de la pupa de BSF tiene el potencial de acelerar la formación ósea al aumentar el número de osteoblastos y reducir el número de osteoclastos después de la extracción dental, lo que sugiere su papel beneficioso en la regeneración ósea.

Palabras clave: *Remodelación ósea; Quitosano; Dípteros; Pupa; Osteoblastos; Osteoclastos.*

INTRODUCTION

Tooth extraction triggers atrophy of the alveolar bone around the tooth socket by about 5-7 mm and 2/3 of this reduction occurs within the first 3 months. The occurrence of atrophy if not treated immediately will result in bone loss vertically and horizontally. In edentulous patients with severe bone loss, the use of bone graft material is essential to restore the lost bone and support future prosthetic rehabilitation.

The classification of sockets can be divided into four types according to the degree of bone loss so that they can be adjusted to post-extraction socket repair.[1,2]

Bone grafting is a surgical procedure used to replace missing bone with material derived from the patient's own body, or with synthetic or natural substitutes for bone. Bone grafts are utilized because bone tissue has the ability to regenerate and grow over time. The classification of bone grafts based on material type is as follows:

a. Allograft: bone grafts involve bone alone or using a combination of other materials (e.g. Grafton, Orthoblasts)

b. Factor-based bone grafts are natural and recombinant growth factors, used alone or in combination with other ingredients such as transforming factor-beta (TGF-Beta), platelet-

derived growth factor (PDGF), fibroblast growth factor (FGF), and

c. Cell-based bone grafts use cells to produce just new tissue or add to the supporting matrix, for example, mesenchymal stem cells.

d. Ceramic-based bone graft substitutes include calcium phosphate, calcium sulfate, and bioglass used alone or in combination; For example, osteograph, proosteon, osteoset.

e. Polymer-based bone grafts use degra-dable polymers that cannot be regarded alone or in combination with other materials, for example, polylactic acid polymers of open porosity.[3]

For a bone graft to be effectively accepted by the body, it must meet several key criteria: it should be biocompatible, support osteoconduction, promote osteoinduction, and possess osteogenic properties. Osteoconduction and osteoinduction are important for biomaterials to promote the formation of bone tissue growth. Bone grafts can be classified as autograft, allograft, xenograft and alloplast. The ideal bone graft material should have the potential to keep cells alive, not cause immunological reactions, be easily available and provide strength to the area around the bone and not spread disease.

Autografts have become the gold standard for successful regenerative procedures because they can support the osteogenic, osteoinductive, and osteoconductive properties associated with preosteoblastic cells in grafts, but autograft bone retrieval can cause several complications, such as blood loss, hematoma formation, fractures, infections, aesthetic disturbances and chronic pain at the site where the bone was removed. An alternative is to use an allograft.[4–6]

In bone tissue engineering innovations, three-dimensional scaffolds are developed that can be absorbed by the body, like polymers that can accelerate the repla-cement of damaged tissue or function as an extracellular matrix, because scaffolds allow cells to proliferate, differentiate and maintain tissue function.

One of the polymers that is currently widely used is chitosan. Chitosan is proven to accelerate bone formation so it is generally used as a scaffold for bone healing management. Chitosan is widely used for cartilage tissue engineering, wound healing and orthopedic treatment applications due to its porous structure and intrinsic antibacterial characteristics. The biocompatibility of chitosan nanofiber membranes and their biological effects on bone regeneration have been previously assessed.

Ho *et al.,*[7] developed chitosan nanofiber scaffolds with beneficial effects on osteoblast proliferation and maturation. Osteoblasts play an important role in bone formation. Our previous studies showed that chitosan nanofibers can stimulate osteoblast proliferation and maturation. Chitosan is a polymer produced from the deacetylation of chitin, consisting of beta[1-4] linked D-glucosamine and N-acetyl-D-glucosamine.[8] Chitosan has high osteo-inductivity, is of easy application, and biodegradability that makes it a good candidate for bone rege neration.[9]

Chitosan-derived compounds include carboxymethyl chitosan, glycol chitosan, cyanoethyl chitosan, aminoethyl-chitosan, dimethylaminoethyl chitosan, diethylami-noethyl chitosan, palmitoyl-trimethyl-chitosan, and N-succinyl chitosan. Chemical modifications and the development of chitosan derivatives have been explored to enhance its properties and expand its applications in biomedical formulations.[10]

Previous *in vivo* studies have demonstrated that carboxymethyl chitosan can enhance osteoprotegerin levels and decrease RANKL in rabbits, resulting in a significantly increased OPG/RANKL ratio (p<0.05). Increased OPG/

RANKL ratio strengthens osteoblast activity, weakens osteoclast activity, promotes osteogenesis, and suppresses osteolysis.[11]

In Indonesia, people often prefer using natural ingredients for prevention and treatment. The government has supported this practice by regulating the use of medicinal herbs in healthcare facilities through various government regulations, ministerial decrees, and laws since 1998 and continuing to the present.[12] This study was conducted to determine the potential of chitosan from BSF pupae in *Cavia cobaya* socket on the influence of alveolar bone formation through the expression of the number of osteoblasts and the number of osteoclasts after tooth extraction.

MATERIALS AND METHODS

This study used a true experimental method with a posttest design only with a control group design. This study used guinea pigs (*Cavia cobaya*) males who fulfilled the criteria of body weight of 200-300 grams, age 2-3 months, and physical health characterized by active movements. A total of 18 *Cavia cobaya* specimens were divided into two groups, placed and acclimatized at room temperature (22°C and 24°C) for seven days at the Animal Biochemistry Laboratory, Faculty of Medicine, Universitas Airlangga, Indonesia. This research was carried out after obtaining Ethical Approval from the Health Ethics Commission of the Faculty of Dentistry, Lambung Mangkurat University No. 042/KEPKG- FKGULM/EC/III/2023.

The first step was to extract chitosan from BSF pupae, through the stages of demineralization using hydrochloric acid, deproteinization using sodium hydroxide, and depigmentation so that chitosan from BSF pupae are obtained and then the deacetylation process is continued to convert chitin into chitosan. Chitosan is produced in the form of a powder preparation with a high deacetylation degree of 80% indicating its purity; then the chitosan was converted into a gel preparation that was applied to the socket after *Cavia cobaya* tooth extraction.

The study subjects consisted of 18 healthy male *Cavia cobaya* which were divided into 2 groups (n=9), the control group (CC) which was not given chitosan BSF (*Hermetia illucens*) pupae gel after tooth extraction, the treatment group given chitosan BSF (*Hermetia illucens*) pupae (CBSF) after tooth extraction with each group observed on the 7^{th}, -14^{th}, -21^{st} days.

Cavia cobaya were anesthetized using ketamine at a dose of 50 mg/kg BB and xylazine at a dose of 5 mg/kg intramuscular body weight then tooth extraction was carried out on the left mandible incision, and the tooth socket was irrigated with sterile aquadest liquid to remove the remaining debris left in the tooth extraction socket, in the CC group after tooth extraction followed by suturing the wound with non-resorbable sutures, while CBSF group after a tooth extraction is applied BSF chitosan pupae gel using a sterile plastic syringe into the socket after extraction until full then followed by suturing the wound with non-absorbable nylon silk sutures so that the wound does not enter the food and not played by its hands.

Euthanasia of experimental animals on the 7^{th}, -14^{th}, -21^{st} days after administering the treatment. The jawbone in the interdental area of the incisive teeth of the mandible is cut and inserted in formalin buffer fixation solution 10 then a procedure for making anatomical histopathological anatomy (HPA) using coloring Hematoxylin Eosin (HE). Histopathological preparations are observed using

a light microscope, observations are carried out on 1/3 apical mandibular socket with an enlargement of 400x on 5 view points.
Osteoblast cells are in the form of cuboidal or flattened cylindrical clusters with single-nucleated cells and bluish-red cytoplasm. Osteoclast cells have a round to oval shape, the cytoplasm is bluish-red. The number of osteoblast cells and osteoclast cells that have been observed per field of view, recorded and analyzed.
The data obtained are tested first using normality and homogeneity tests. The normality test uses the Shapiro-Wilk test because the number of data is less than 50 and the homogeneity test uses Levene's Test.

Normal and homogeneous distributed research data (p>0.05) were analyzed using parametric analysis with one-way ANOVA to see significant differences between treatments. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean±SD osteoblasts in the CBSF group and CC group at observations on the 7th, -14th, and -21st days, Figure 2. Histopathological examination was obtained on the 7th, -14th, and -21st days respectively as shown below:
An increase in the number of osteoblasts will accelerate bone repair and formation. Osteoblast expression levels were highest on day 21 in the CBSF group (104.13±5.33), while the lowest occurred in the CC group (39.80±5.43) on day 7 (Figure 1).
The osteoblast expression is higher in the CBSF group than in the CC group. The results

Figure 1
Synthesis process and making black soldier fly pupae chitosan gel

Figure 2

Diagram of the average number of osteoblast cells in the post *Cavia cobaya* extraction socket on the 7th, 14th, and 21st days. The figure above shows an increase in the number of osteoblast cells in the CBSF group compared to the C group on the 7th, 14th, and 21st days

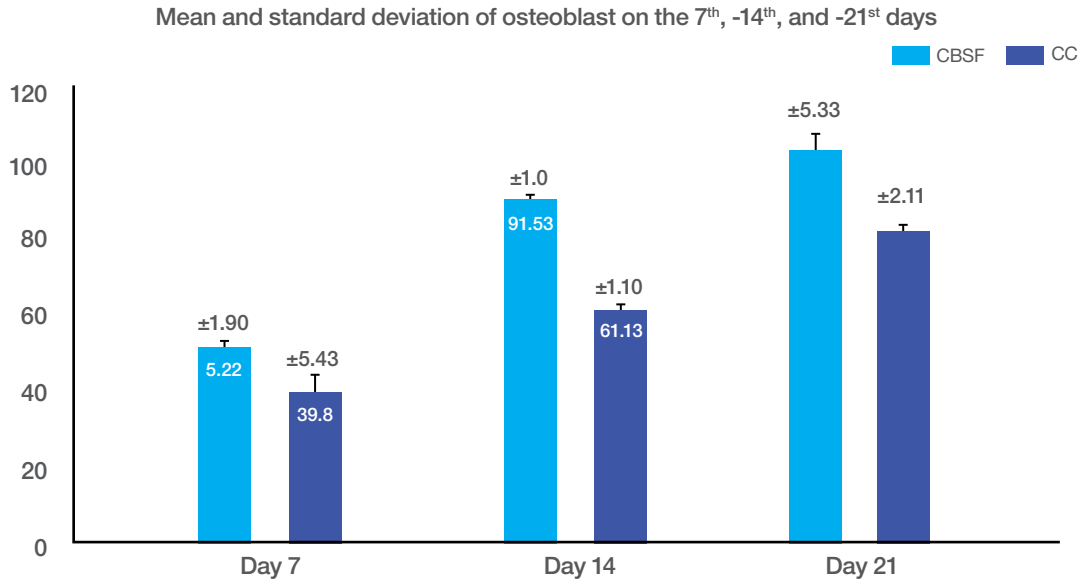

Figure 3

Histopathologically described *Cavia cobaya* osteoblast cells in the control group (C) and the chitosan pupa BSF (CBSF) application group under a light microscope at 400x magnification on the 7th, 14th, and 21st days

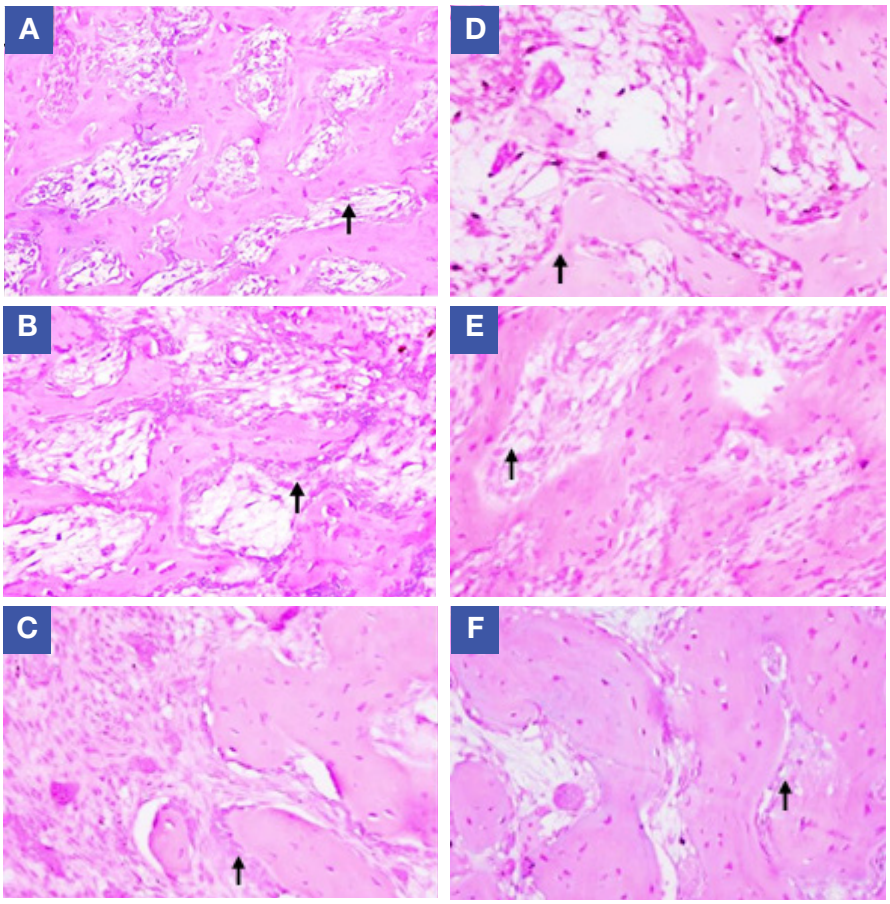

Figure 4

Diagram of the average number of osteoclast cells in the post *Cavia cobaya* extraction socket on the 7th, 14th, and 21st days

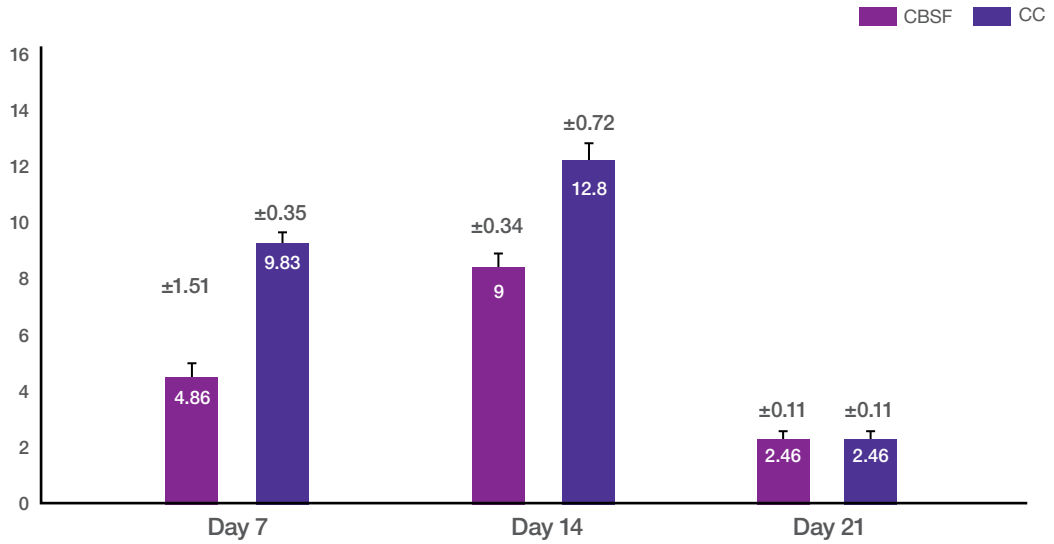

Figure 5

Histopathologically described Cavia cobaya osteoclast cells in the control group (C) and the chitosan black soldier fly (CBSF) application group under a light microscope at 400x magnification on the 7th, 14th, and 21st days

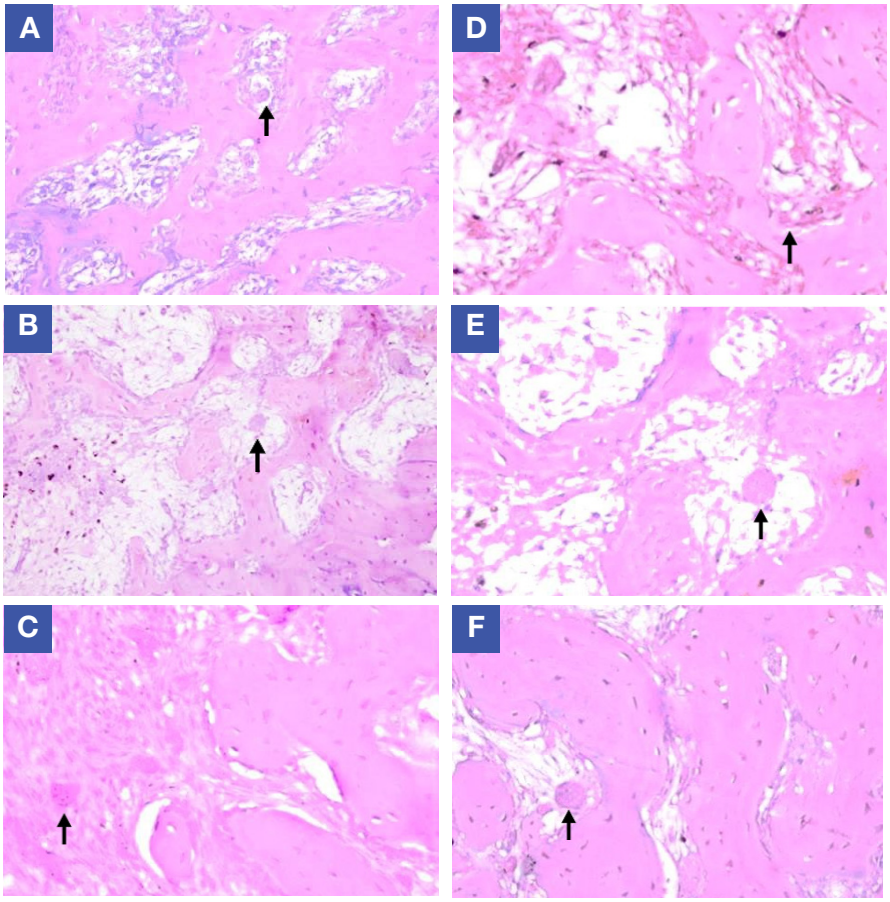

Table 1
Post-extraction tooth socket classification

Class	Description
Class I	4-wall defect, intact bony housing, no wall involvement.
Class II	3-wall defect, 3 intact walls, 1 wall with dehiscence;
Class III	or fenestration.
Class IV	Type 1: adequate height, inadequate width;
	Type 2: 2 intact walls, 2 walls with dehiscence or fenestration 1-wall defect, inadequate vertical height, inadequate horizontal

of this study proved that BSF chitosan pupae were able to increase the number of osteoblasts from the 7th, -14th, and -21st days compared to the control group that was not given BSF chitosan pupae gel.

The results of osteoblast cell calculations were processed and analyzed using normality tests, namely the Shapiro-Wilk test and variance homogeneity tests using Levene's Test. The normality test result shows 0.035 (p>0.05) in each group which means the distribution of data is normally distributed.
The data is normally distributed, so the homogeneity test of variance Levene's Test obtained a result of 0.027 (p<0.05) meaning that different data variances show inhomogeneous data. Normal distributed data and different data variants were then continued with data analysis using Oneway ANOVA parametric analysis with a confidence level of 95%. In the Oneway ANOVA parametric test, it was found that there were differences in the CBSF group and CC group on the 7th, -14th, and -21st days with a value of p= 0.000 (p<0.05).

The number of osteoclasts decreased on days 7th, 14th, and 21st. The greatest reduction in osteoclast numbers was observed on day 21, with the CBSF group showing the lowest mean value (2.66±0.11), followed by the CC group (2.46±0.11). The results of osteoclast cell calculations were processed and analyzed using the normality test with the Shapiro-Wilk test (p>0.05).
The results of the normality test showed the data was not normally distributed, so the statistical test using the Kruskal Wallis test was carried out. The results of the Kruskal Wallis chitosan black soldier fly test obtained a significance result of p=0.006.

DISCUSSION

The wound healing process is classically described as a sequence of overlapping phases: inflammation, proliferation, maturation, and remodeling. The inflammatory phase involves the removal of necrotic tissue and the prevention of infection by pathogenic microorganisms. This is followed by the proliferative phase, characterized by macrophage-mediated phagocytosis and the subsequent recruitment of fibroblasts responsible for collagen synthesis.

The maturation phase aims to optimize tissue organization and tensile strength through epithelialization and scar formation. Finally, the remodeling phase involves collagen reorganization and degradation as healing is

completed. The normal healing response is initiated following tissue injury.[13] Chitosan is derived from chitin which through the deacetylation process is a linear, semi crystalline polysaccharide consisting of (1 → 4) -2-acetamido -2-deoxy-b-d-glucan (N-acetyl D-glucosamine) and (1 → 4) -2- Amino-2-deoxy-β-d-glucan unit (D-glucosamine).

The degree of deacetylation (DD) is often used to express the number of amino groups in chitosan. The degree of deacetylation also impacts the biocompatibility of chitosan. For example, higher DD increases the amount of positive charge and interaction between chitosan and cells, resulting in improved biocompatibility.[14] Chitosan is a copolymer of D-glucosamine and N-acetyl-D- glucosamine with a β-(l-4) bond, obtained from alkali or enzymatic deacetylation of the polysaccharide chitin. Chitosan has the chemical name Poly N-acetyl-D-glucosamine (or beta(1-4) 2-acetamido-2-deoxy-D-glu-cose). The chitosan structure has -OH and -NH2 groups that can produce intra- and inter- molecular hydrogen bonds.

These chitosan groups can interact or covalently bond and become the basis of drug delivery techniques. The difference between chitin and chitosan is that in each ring of the chitin molecule, there is an acetyl group (-CH3- CO) on the second carbon atom, while in chitosan there is an amine group (-NH). The majority of chitosan's biological properties are related to its cationic activity and the size of its polymer chains. These characteristics make chitosan ideal for use as a wound dressing. The main biochemical activities of chitin and chitosan-based materials in the wound healing process are through polymorphonuclear cell activation, fibroblast activation, cytokine production, giant cell migration, and stimulating type IV collagen synthesis. Chitosan biopolymers effectively depolymerize to release N-acetyl-β-D-glucosamine to initiate fibroblast proliferation during the wound healing process.[9,15] This study showed an increase in the number of osteoblasts on the 7th day and continued to increase on the 14th day and 21st day.

The amino and hydroxyl clusters of the chitosan molecules can react with unstable free radicals and form stable macromolecules. The chitosan BSF pupae in this research has a degree of deacetylation of 80-90%, which can be categorized as high deacetylated chitosan so that it can provide a relatively good antioxidant effect on osteoblasts under oxidative stress conditions. Chairani *et al.*,[16] concluded that chitosan application to osteoblast cultures reportedly increased collagen, alkaline phosphatase, and osteocalcin which represent proteins that play a role in bone remodeling. Chitosan can also stimulate osteoblasts to synthesize and secrete a certain amount of protein, therefore the total protein concentration will increase.

Sukul *et al.*,[17] concluded that the degree of deacetylation of chitosan seems to be the main characteristic of chitosan in determining cell attachment behavior in regulating the secretion of bone markers and cytokines. The higher degree of deacetylation indicates the purity of chitosan and the higher cell spread. Chitosan with a high degree of deacetylation can induce osteopontin which is an osteoblast-derived secretor protein that plays a role in bone remodeling, osteoblast response, and increased inflammation on the 21st day.
Osteoprotegerin (OPG) is a secreted protein involved in bone density regulation by inhibiting osteoclastogenesis and asso-

ciated bone resorption in this study, chitosan may also increase osteoprotegerin and sclerostin secretion on the 14th day. Chitosan with a high degree of deacetylation can facilitate osteoblast differentiation and extracellular matrix production, whereas chitosan with a low degree of deacetylation stimulates the secretion of factors that favor osteoclastogenesis.

This study showed a decrease in the number of osteoclasts on the 7th, -14th, -and 21st days. Chaesarina *et al.*,[18] concluded that chitosan will progressively decrease the production of inflammatory cytokines namely IL-1, IL-6 and TNF-α which play a role in the differentiation and activation of osteoclasts directly through RANKL (Receptor Activator of Nuclear kβ Ligand). Prostaglandin E2 and proinflammatory cytokines are also able to inhibit the formation of OPG which functions to inhibit the formation of osteoclasts. This causes the formation and activity of osteoclasts to be disrupted, thereby reducing the rate of bone resorption so that the number of osteoclast cells decreases.

Activation of osteoclast cells in bone resorption begins with the release of M-CSF (Macrophage-Colony Stimulating Factor) which will bind to the receptor c-Fms contained in osteoclast precursors to stimulate differentiation and proliferation of hematopoietic progenitors into pre-osteoclasts which then express RANK (Receptor Activator of Nuclear Factor Kβ). Osteoblast cells and stromal cells produce OPG that will bind to RANKL (Receptor Activator of Nuclear Factor kβ Ligand). OPG and RANK bonds inhibit RANK and RANKL bonds, so osteoclast cell formation does not occur in the bone remodeling process.

The repair of bone defects depends on several factors such as the proliferation of bone progenitor cells and bone growth factors. In bone tissue engineering, bone replacement plays an important role in supporting cell adhesion, growth, and proliferation at the injury site.

Chitosan is similar to glycosaminoglycan which is a natural component of the extracellular matrix that forms cell growth and supports the proliferation, differentiation and mineralization of osteoblasts. *In vitro* studies have shown that chitosan can increase the adhesion and proliferation of osteoblasts and mesenchymal stem cells. Chitosan may also promote the growth of human bone marrow mesenchymal stem cells by promoting the expression of genes associated with osteogenesis and calcium-binding proteins, such as type I collagen, integrin-binding salivary proteins, osteopontin, osteonectin , and osteocalcin.[14]

Ueno *et al.*,[19] also concluded that stimulation of macrophage cells using chitosan showed an increase in TGF β1, PDGF, VEGF and FGF-2 to enter the proliferation phase. FGF-2 plays an important role in granulation tissue development, fibroblast proliferation, epithelial cell proliferation and angiogenesis. Growth factors are also released by platelets and fibroblasts, including FGF-2 produced by monocytes, keratinocytes and fibroblasts. This phase results in the development of tissue that will eventually be replaced by bone. When tissue is resorbed, cells such as fibroblasts, chondroblasts, and osteoblasts will begin to form by pluripotent mesenchymal cells.

Fibroblast tissue will stimulate OPG to inhibit RANKL binding to RANK and trigger FGF-2 growth. Osteoprotegerin will also express the transcription factor, Runx2, which is the earliest osteoblast marker and will affect

mesenchymal cells and osteoblast cells and modulate Runx2 expression to help osteoblasts formation.[19,20]

CONCLUSIONS

The application of black soldier fly pupae chitosan has the potential to accelerate bone formation through an increase in the number of osteoblasts and reduces the number of postextraction osteoclasts in *Cavia cobaya*, which may aid in the regeneration of bone.
Although these results suggest possible relevance to human applications, further research involving other bone formation biomarkers is necessary.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest relevant to this study.

ETHICS APPROVAL

This research was carried out after obtaining ethical approval from the Health Ethics Commission of the Faculty of Dentistry, Lambung Mangkurat University No. 042/KEPKG-FK GULM/EC/III/2023.

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AUTHORS' CONTRIBUTIONS

Renie Kumala Dewi: Conceptualization; Methodology; Data curation; Funding acquisition; Project administration. Writing – original draft; Writing – review & editing.

Sri Oktawati: Data curation; Investigation; Methodology; Supervision.Writing – original draft; Writing – review & editing.

Asdar Gani: Data curation; Investigation; Supervision. Writing – original draft; Writing – review & editing.

Eko Suhartono: Data curation; Investigation; Software; Supervision. Writing – original draft; Writing – review & editing.

Ni'mal Maula: Resources. Writing – original draft; Writing – review & editing.

Nurlindah Hamrun: Validation; Visualization. Writing – original draft; Writing – review & editing.

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