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The Formulation of Combination Nanochitosan *Black Soldier Fly (Hermetica Illucens)* Pupae and *Demineralized Dentin Matrix* (DDM) from Human Teeth Promotes Accelerated Bone Remodeling

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ABSTRACT

Background. Tooth extraction is a procedure to remove teeth from inside the socket which can cause damage to the tooth socket area. Black Soldier Fly (BSF) (*Hermetia illucent*) contains as much as 35% chitin found in shedding and cocoons. Chitin can be converted to chitosan. Nanochitosan is the smallest part of chitosan. Chitosan has high osteoconductivity properties that promote bone regeneration. Demineralized Dentin Matrix (DDM) came from human teeth that have been extracted is an organic material obtained from dentin that has osteogenic capabilities. **Objective.** To determine the potential of the combination of nanochitosan BSF pupae and DDM in forming RANKL, and OPG after tooth extraction. **Metode.** The left mandibular incisive tooth guinea pig is extracted, then the socket is filled with a Polyethylene glycol gel as a placebo in the control group (n=9), and the treatment group (n=9) is filled with a combination of nanochitosan BSF pupae and DDM from human teeth gel. The gel is inserted into the socket until it is full then suture with non-absorbable silk. The guinea pig in euthanasia saw the expression of RANKL, and OPG on the 7th, 14th, and 21st days. The RANKL, OPG, and Osteocalcin research results using Oneway ANOVA ($p<0.05$).

Result. There is a significant difference between the treatment and control group with the significance value in the expression RANKL, OPG (0.000) ($p<0.05$). **Conclusion:** Combination of nanochitosan BSF pupae and DDM from human teeth has an effect in increasing the expression of Osteoprotegerin (OPG) and decreasing RANKL on the -7th, -14^{th,} and -21st days and might help increase bone remodeling.

Keywords: *Bone Remodeling, Demineralized Dentin Matrix (DDM), Nanochitosan.*

INTRODUCTION

Tooth extraction is the extraction of intact teeth without causing pain with minimal trauma to the supporting tissues so that the wound due to tooth extraction will heal normally and do not cause complications. Teeth need to be extracted for a variety of reasons, some of which are the persistence of the first tooth and supernumerary teeth or crowding teeth, teeth with deep caries, teeth located at the fracture line, impacted teeth, orthodontic purposes, prosthetic purposes, before radiotherapy treatment, and residual roots. Within one-year post-extraction, there is an average ridge decrease of 50%. The average amount of loss between 5-7 mm and 2/3 of the bone loss occurred in the first 3 months and showed the same pattern in all areas of the oral cavity. Tooth sockets after extraction need to be treated immediately to prevent resorption of the alveoli bone. Efforts to improve bone regeneration in alveolar bone defects around the tooth socket can use several types of bone graft materials. The conditions that must be met by a good bone graft are that it is acceptable to the body or biocompatible, has the properties of osteoconduction, osteoinduction, and osteogenesis of bones. Osteoconductive and osteoinductive are the most important for biomaterials to promote bone tissue growth.[1,2]

In bone tissue engineering innovations, three-dimensional scaffolds were developed that can be absorbed by the body like polymers, which can accelerate the replacement of damaged tissues or function as extracellular matrices, because scaffolds

allow cells to proliferate, differentiate, and maintain tissue function. One of the polymers that are currently widely used is chitosan. In general, insects that are used as a source of chitin are beetles and silkworms. In the prepupa phase, until it becomes a pupa, BSF flies can be used as a potential source of chitin because the exoskeleton of the BSF fly contains as much as 35% chitin found in shedding and cocoons. Chitin can be converted to chitosan through the process of deacetylation. Chitosan is a natural polysaccharide synthesized from chitin extracted from animal shells. The characteristics of chitosan obtained are highly dependent on the effectiveness of the deacetylation stage and the source of chitin used. BSF (*Hermetia illucens*) has a fairly high protein content of around 40 – 50%. The healing of soft and hard tissues is mediated by a variety of intracellular and extracellular events regulated by protein signals.[2,3]

The capabilities of chitosan applied in various fields of modern industry, such as pharmaceuticals, biochemistry, cosmetics, food industry, and textile industry, encourage the continued development of various research using chitosan, including chemically or physically modifying chitosan. Physical modifications in chitosan include changing the size of chitosan particles or granules to become smaller for wider utilization, and the development of physical and chemical modifications leads to the shape of nanoparticles. Nanoparticles have advantages compared to similar materials in large sizes (bulk) because the size of nano-particles has a greater ratio value between surface area and volume when compared to similar materials in large sizes, so nano-particles are more reactive. Nanochitosan which is a small part of chitosan, chemically chitosan is a linear polysaccharide that has a chain in the form of β-(1,4)-2-amino-2-deoxy-D-glucopyranose which is similar in structure to glucosaminoglycan (GAG). GAG plays an important role in wound healing. The capabilities of chitosan applied in various fields of modern industry, such as pharmaceuticals, biochemistry, cosmetics, food industry, and textile industry, encourage the continued development of various research using chitosan, including chemically or physically modifying chitosan. Physical modifications in chitosan include changing the size of chitosan particles or granules to become smaller for wider utilization, the development of physical and chemical modifications leads to the shape of nanoparticles. Nanoparticles have an advantage compared to similar materials in large sizes (bulk) because the size of nano-particles has a greater ratio between surface area and volume when compared to similar materials in large sizes, so nano-particles are more reactive.[4,5]

However, chitosan has weaknesses such as low mechanical strength and lack of active sides that can improve the working function of the membrane, to overcome these weaknesses it is necessary to modify one of them with other natural materials such as Demineralized Dentin Matrix (DDM) derived from human teeth. Bone and dentin have the same composition, which is 70% hydroxyapatite, 18% collagen, 10% body fluids, 2% non-collagen proteins. In bone and dentin, several growth factors that cause dentin can trigger osteoinduction, osteoconduction, and the formation of blood vessels.[6,7]

Demineralized Dentin Matrix (DDM) is a bone graft material found in human dental dentin. The advantages of using this material are that it has osteoconductive and osteoinductive abilities, reduces the use of anesthesia, efficiency of operation time, reduces the loss of more blood and does not require surgery on other parts of the patient's body.[8]

The act of tooth extraction will leave a wound in the form of an open tooth socket and cause discomfort for patients, especially in pediatric patients, so it is necessary to make a material that can speed up the wound healing process by providing a material to help the healing, this studi aims to process through the application of ingredients derived from a combination of Black Soldier Fly nanochitosan (*Hermetia illucens*) and Demineralized Dentin Matrix (DDM) in wounds after tooth extraction has never been done so it is expected to be a future biomaterial that can accelerate the process of alveolar bone formation by looking at RANKL to prevent/decrease the inflammatory process and prevent alveol bone resorption and see OPG which stimulate osteoblastic activity in alveolar bone formation.

MATERIAL AND METHODS

This study uses a true experimental method with posttest only with a control group design and has passed the ethics test with number 0108/PL.09/KEPK FKG-RSGM UNHAS/2023. The first step is to make chitosan BSF pupa through the stages of demineralization, deproteinition, and depigmentation so that BSF pupa chitin is obtained and then followed by a deacetylation process to convert chitin into chitosan. Chitosan is self-produced as a powder preparation with a degree of deacetylation of 80% indicating chitosan purity. Chitosan is transformed into a gel preparation that will be applied to the socket after cavia trial tooth extraction by mixing nanochitosan of BSF pupae powder (NBSF)+Demineralized Dentin Matrix (DDM) powder (50:50 ratio) and PEG 400 and PEG 4000 until homogeneous. The study subjects consisted of 18male Cavia cobaya with inclusion criteria aged 3-4 months with a weight of 300-375 grams declared healthy at a physical examination by a veterinarian and criteria for exclusion of dead animals before research, which was divided into 2 groups, namely the control group (C) which was not given a combination of NBSF+DDM gel and the treatment group (T) which was given a combination of NBSF+DDM gel with each group being observed at 7, -14 and 21 days.

Animals were tried to be anesthetized using ketamine at a dose of 50 mg/kgBB and xylazine at a dose of 5 mg/kgBB intramuscularly then tooth extraction was carried out on the left mandibular incisive, and the tooth socket was irrigated with sterile aquadest fluid to remove the remaining debris left in the tooth extraction socket, in the control group (C) after tooth extraction followed by wound suturing with non-resorbable sutures, while the treatment group (T) after tooth extraction was applied NBSF+DDM gel using a sterile syringe into the socket after the extraction until it was full, then sutured the wound with non-resorbable sutures. Euthanasia of experimental animals on the -7th, -14^{th,} and -21st days after treatment. To detect the bone regeneration process, after the -7th, -14^{th,} and -21st days, alveolar bone was taken in the socket area after tooth

extraction for the manufacture of paraffin blocks and slide preparations. Furthermore, an examination was carried out with Hematoxylin Eosin (HE) staining to see the presence of osteoblast cells and the calculation of the number of osteoblast cells, as well as the CPI (Immunohistochemical) staining technique to see the number of osteoblasts that can express RANKL, and OPG. The immunohistochemical staining technique (CPI) was carried out on bone tissue preparations using anti-RANKL, and anti-OPG monoclonal antibodies.

The calculation of RANKL, OPG expressions was carried out using a light microscope with a magnification of 400x in the area of one third of the apical of the tooth socket, calculation by looking at 5 fields of view. The data obtained were tested first using the normality test using Shapiro wilk (P>0.05) and homogeneity with the levene test. Then continued with the test a Oneway ANOVA (p<0.05) comparative test is carried out, the data analysis is then continued with the postHoc Bonveroni test to find out which groups provide statistically significant differences.

RESULT

The mean and standard deviation of RANKL, and OPG expressions in the control group and the treatment group on the 7th, -14th, and -21st day observations can be seen in Figure 1, 2 and 3.

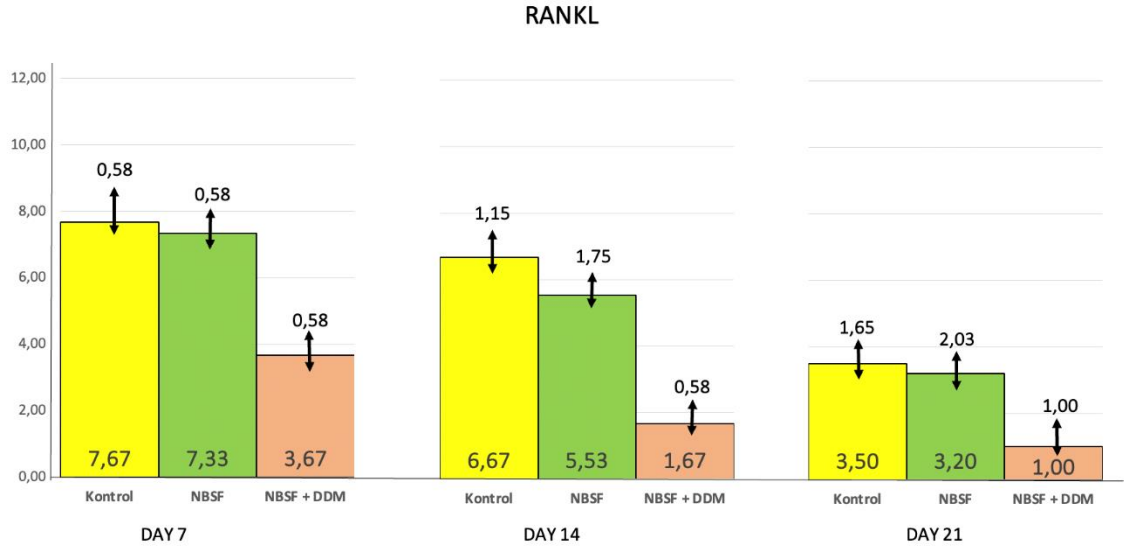


Figure 1. Graph of RANKL expression measurement results in each sample group on the 7th, -14th, and -21st day.

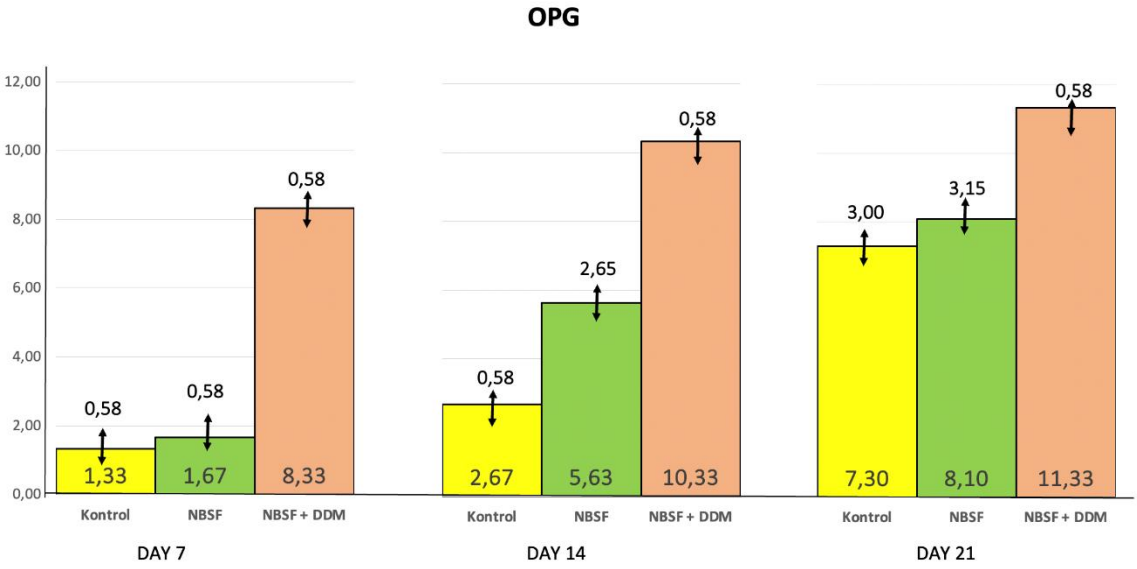


Figure 2. Graph of the results of OPG expression measurements in each sample group on the 7th, -14th, and -21st day.

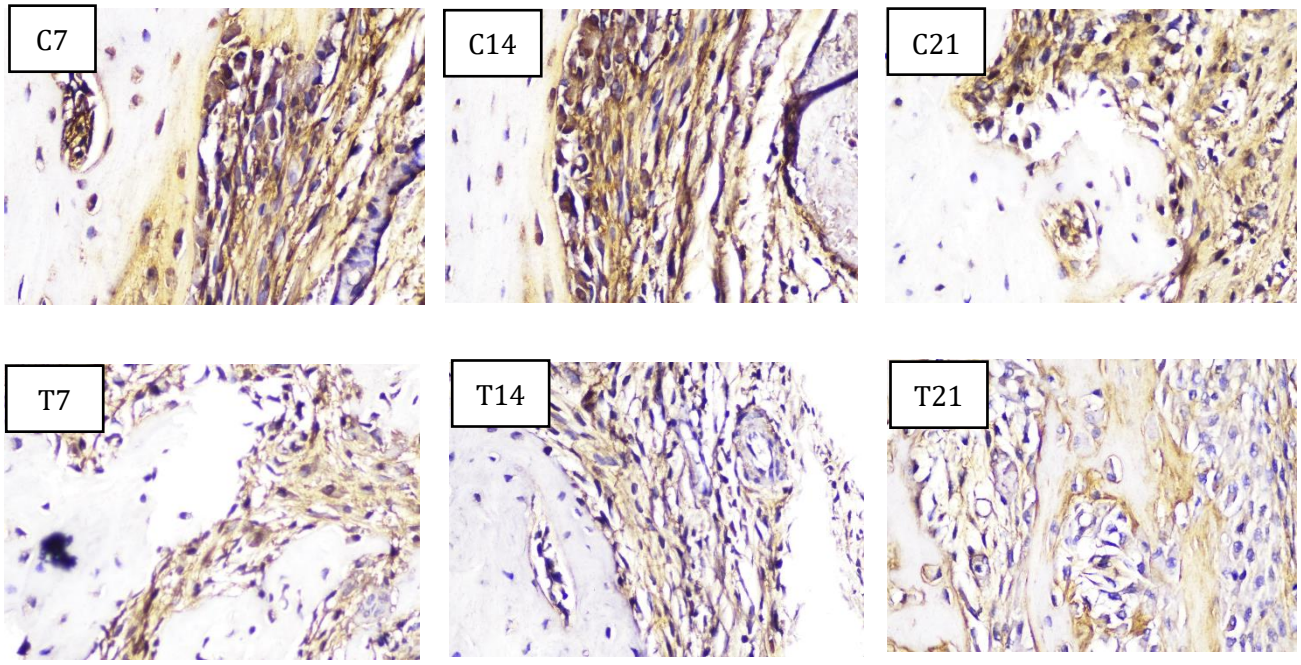


Figure 3. Overview of IHC of RANKL within the socket of guinea pig (*Cavia cobaya*) teeth post-extraction in the treatment (T) group and control (C) group under a light microscope at 400x magnification on the 7th, 14th, and 21st days.

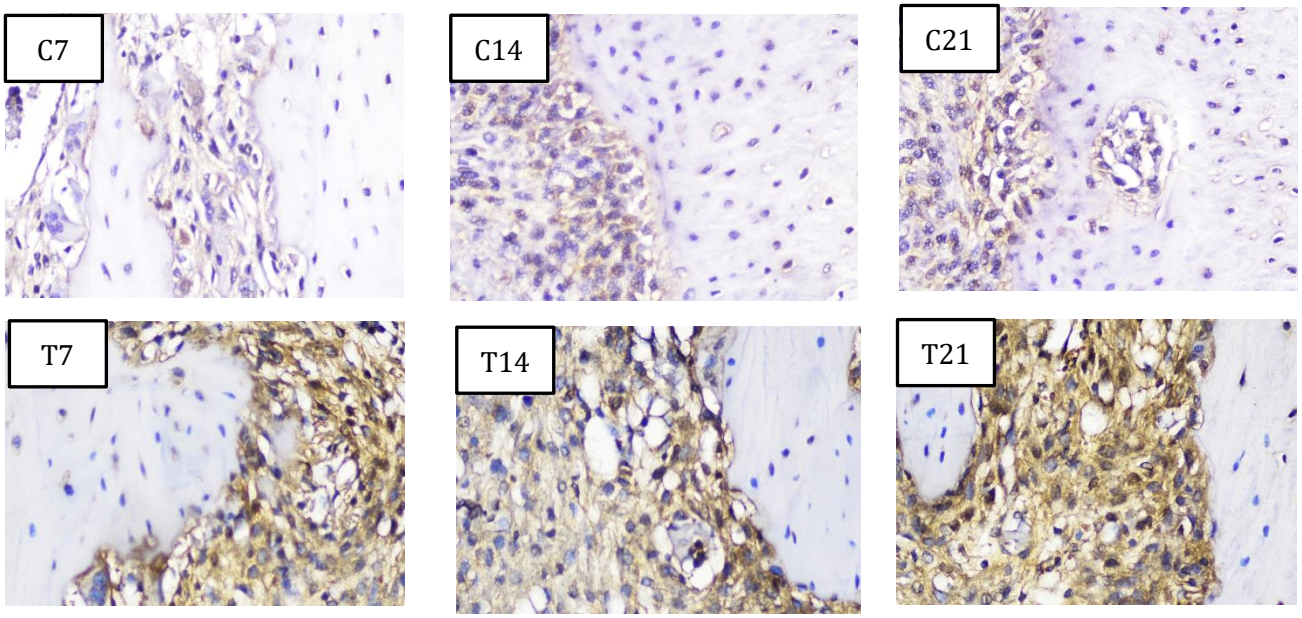


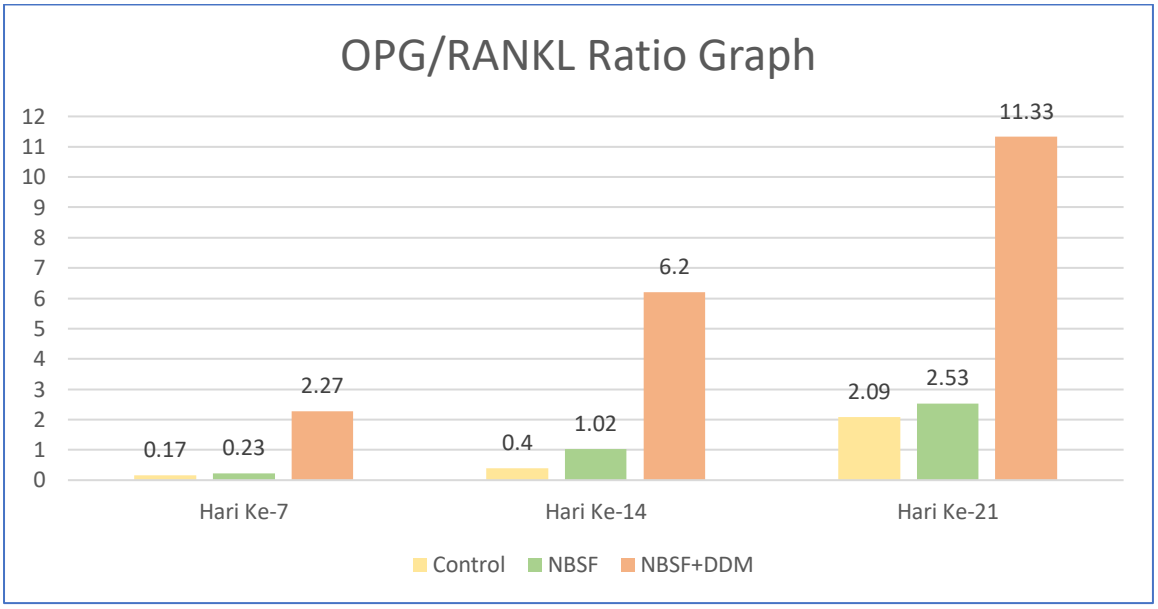
Figure 5. Overview of IHC of OPG within the socket of guinea pig (*Cavia cobaya*) teeth post-extraction in the treatment (T) group and control (C) group under a light microscope at 400x magnification on the 7th, 14th, and 21st days.

The Oneway ANOVA test showed that there was a significant difference between groups (0.000) ($p<0.005$), so it can be said that there was a significant difference between groups.

Table 2. Oneway ANOVA Test

	Anova
RANKL	0.000
OPG	0.000

Based on the table above, the group that was given treatment had a higher OPG/RANKL ratio compared to the control group. The treatment group with NBSF+DDM on day 21 had the highest OPG/RANKL ratio of 11.33 and the lowest OPG/RANKL ratio in the control group on day 7 of 0.17, which means that the NBSF+DDM application group on day 21 had the most OPG expression.



DISCUSSION

The healing process of tooth extraction wounds in principle consists of the process of inflammation, proliferation and remodeling.[9] Some proteins that have an important role in this matter are Receptor Activator of Nuclear Factor κB Ligand (RANKL), and osteoprotegerin (OPG). RANKL is a homotrimeric type II transmembrane protein that is expressed as a secretion protein and surrounds the membrane, derived from proteolytic cleavage. RANKL expression is stimulated in osteoblasts/stromal cells through several known factors to stimulate the formation and activity of osteoclasts.[10] Osteoprotegerin (OPG) is a glycoprotein produced by human periodontal ligament cells and is a key factor in the inhibition of differentiation and activation of osteoclasts. OPG also acts as a RANKL receptor that competes with RANK to bind and avoid interaction with RANK, resulting in inhibition of osteoclastogenesis.[11] While osteocalcin (OCN) is a protein synthesized by osteoblasts that bind to hydroxyapatite in the bone matrix.[12] Hydroxyapatite has good osteoconductive properties, so the production of osteoblasts can be increased.[13]

The results of the combined NBSF+DDM showed that there was a decrease in RANKL expression, an increase in OPG expression compared to the control group and the NBSF group on the 7th, 14th, and 21st days. This study shows that there is a significant difference between the control group and the NBSF+DDM group. This is because chitosan can decrease the production of pro-inflammatory cytokine mediators namely IL-1, IL-6 and TNF-α which play a role in the differentiation and activation of osteoclasts through RANKL. Chitosan when it encounters inflammatory cells will release N-acetyl-Dglucosamine and bind to major receptors on macrophages and trigger the migration of inflammatory cells to the wound area and increase the proliferation of inflammatory cells in the wound area. The increasing proliferation of inflammatory cells causes more cytokines and growth factors to be released by these inflammatory cells. Some of the cytokines and growth factors that play an important role in the wound epithelialization process are from the EGF (Epidermal Growth Factor) and HB-EGF (Heparin Binding EGF); FGF family, TGFβ1 (Transforming Growth Factor β1); and KGF (Keratinocyte Growth Factor).[14]

This study is in line with an *in vitro study* conducted by Kazimierczak (2021) showing that after 7 days, macrophages cultured on the chitosan surface release significantly higher amounts of IL-4 and TGF-β1 than M0, M1, and M2 macrophages. It is known that IL-4 is included in osteotrophic factors, playing an important role in bone metabolism. In addition, IL-4 lowers osteoclast precursors. In turn, TGF-β1 supports the proliferation and differentiation of osteoblasts as well as the production of extracellular matrix (ECM). In addition, high levels of TGF-β1 increased the expression and secretion of OPG (the feed receptor for RANKL), suppressing RANKL-RANK-mediated osteoclastogenesis.[15]

Chitosan which has high deastilization can improve biocompatibility for the healing process especially the formation of odontoblast cell counts. Biodegraded chitosan plays a role in biological processes including cell interactions, cell-matrix, and also factors involved in growth such as growth factors and bone morphogenetics that will stimulate the differentiation of osteoblastic cells. Chitosan can also be able to directly stimulate multipotent mesenchymal progenitors and

osteogenic cells. Chitosan stimulates the differentiation of osteogenic cells and therefore has real potential to accelerate bone regeneration. Chitosan can also activate inflammatory cells such as macrophages, PMNs, and fibroblasts.[16]

Chitosan has a positive charge from the results of the N-acetyl-D-glucosamine deacetylation process to form D-glucosamine to provide free amino groups to its molecular structure. Nano-sized chitosan can be a drug carrier that targets tumor tissue and has many other biomedical uses. The smaller the particle size, the greater the particle surface area, and thus the greater the chitosan capacity. Due to their small size, nanoparticles can penetrate areas that may not be accessible to other delivery systems such as deep socket retraction scar wounds. This system reduces the frequency of dosing and further provides uniform distribution of the active substance over a long period. The cationic properties of chitosan are used to induce hemostasis because the surface of platelets and erythrocytes shows a hemostat charge due to the presence of phosphatidylcholine, phosphatidledletanolamine, and sialic acid groups. The amino group present in chitosan (poly-N-acetyl glucosamine) is involved in facilitating erythrocyte aggregation through electrostatic interaction with its surface charge, and subsequently, hemostasis is induced after activating platelets. The molecular weight and degree of deacetylation achieved during the chitosan purification process will have a significant effect on the hemostatic ability of chitosan. Higher degrees of deacetylation (DD) increase the aggregation of erythrocytes and platelets required to initiate hemostasis. in nanochitosan pupa BSF, this study has a high deacetylation of 80%. The results showed that the results of DD chitosan pupa BSF met the SNI quality standard No.7949-2013, which was ≥ 75%. According to Natalia's (2021) reseach, a DD value of 40%-100% can be said to be chitosan. The higher the DD, the better the quality of chitosan. The large number of acetyl groups can decrease the quality of chitosan. The higher the quality of chitosan, the higher the purity level. The purity of chitosan can be seen from the low moisture content and ash content with a high degree of deacetylation. The higher the degree of deacetylation, the more amino groups in the chitosan molecular chain so that chitosan will be more reactive. Higher amounts of chitosan DD can also increase the amount of positive charge which increases the interaction between chitosan and cells, leading to increased biocompatibility. Biocompatibility is the ability of a material to interact with living cells/tissues or metabolic systems that do not cause toxicity. DD is affected by the duration and deacetylation temperature, the higher the temperature increases the motion between molecules so that the rate of acetyl group reaction break-up reaction runs faster.[17,18]

The results of this study showed that the NBSF+DDM group had the highest average for OPG expression than the control group and NBSF on days 7, -14 and -21, because NBSF+DDM had DDM. DDM derived from human teeth has the same biochemical composition as bone which is mostly composed of organic and inorganic elements. Bone and dentin have the same composition, which is 70% hydroxyapatite, 18% collagen, 10% body fluids, 2% non-collagen proteins. In bone and dentin, BMPs (*Bone morphogenetic proteins*), FGFs (*Fibroblast growth factors*), type I collagen and type III collagen are also found as protein matrices that are included in non-collagen proteins. Some of these growth factors that cause dentin can also trigger osteoinduction, osteoconduction, and vascular formation.[8,19] This study is in line with Ding's (2020) research that the administration of DDM can increase the formation of new bone and increase the ratio of alveol bone height in the area where the dental implant is implanted in the 4th week.[20]

RANK receptors are expressed in hematopoietic osteoclast progenitors. OPG and RANK are receptors that show the same attractive attraction to RANKL. OPG produced by osteoblasts acts as a RANKL receptor, and prevents RANKL from binding to RANK and activating RANK to inhibit osteoclastogenesis that inhibits osteoclast development. The biological effects of OPG on bone cell cells include inhibition in the late stage of osteoclast differentiation, suppression of activation of mature osteoclasts, and induction of apoptosis, so it can be said that bone remodeling is mainly controlled by the balance of RANKL and OPG.[21,22]

Considering the limitations of this research, it makes sense to conclude that there is an increase in the OPG ratio greater than the rank showing the acceleration of bone remodeling but still need research on the acceleration of bone remodeling by looking at other bone formation markers.

CONCLUSION

The combination of nanochitosan BSF pupae and DDM from human teeth has an effect in increasing the expression of Osteoprotegerin (OPG), and decreasing RANKL on the -7th, -14$^{th.}$ and -21st days and might help increase bone remodeling.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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