EFFECTIVENESS OF FUCOIDAN IN STIMULATING OSTEOBLAST CELLS IN BONE REGENERATION

RESEARCH PAPER OF LITERATURE REVIEW

Submitted to Hasanuddin University to Complete One of the Requirements to Achieve a Bachelor's Degree in Dentistry

DARANISA WULAN PURNAMASARI

J011191098

ORAL BIOLOGY DEPARTEMENT

FACULTY OF DENTISTRY

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HALAMAN PENGESAHAN

Judul : Effectiveness Of Fucoidan In Stimulating Osteoblast Cells In Bone Regeneration

Oleh : Daranisa Wulan Purnamasari / J011191098

Telah diperiksa dan disahkan

Pada tanggal 12 September 2022

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KATA PENGANTAR

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Dalam penulisan skripsi ini terdapat banyak hambatan yang penulis hadapi, namun berkat bantuan dan bimbingan dari berbagai belah pihak sehingga akhirnya, penulisan skripsi ini dapat terselesaikan dengan baik. Oleh karena itu, pada kesempatan ini, dengan segala kerendahan hati penulis ingin menyampaikan terima kasih kepada:

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Makassar, 12 September 2022

Hormat kami,

Penulis

EFEKTIVITAS FUCOIDAN DALAM MERANGSANG SEL-SEL OSTEOBLAS PADA REGENERASI TULANG

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ABSTRAK

Latar Belakang: Terdapat beberapa kasus yang berhubungan dengan kerusakan tulang dalam rongga mulut seperti komplikasi akibat pencabutan gigi dan periodontitis yang berujung dengan kehilangan tulang alveolar. Rekayasa jaringan mampu mengembalikan dan memperbaiki fungsi dari jaringan yang hilang maupun rusak. Salah satu biomaterial yang berperan dalam proses regenerasi tulang yaitu fucoidan dari biopolymer laut alga cokelat yang mempunyai kandungan biomaterial yang dapat membuat sel osteoblas baru. **Tujuan**: Secara umum, *literature review* ini bertujuan untuk mengetahui bahwa fucoidan dapat dimanfaatkan dalam merangsang pertumbuhan sel-sel osteoblas pada regenerasi tulang. **Hasil**: Dari jurnal yang telah di review didapatkan bahwa fucoidan bermanfaat sebagai makanan fungsional dan menjadi obat osteoporosis, mencegah keropos tulang, mempromosikan pembentukan tulang secara in vitro dan in vivo juga menghambat resorpsi tulang yang berlebihan. **Kesimpulan:** Review ini telah menunjukkan bahwa Fucoidan diketahui memiliki aktivitas biologi seperti antikoagulan dan antitrombotik, antioksidan serta berperan sebagai penanda fenotipik pada tahap awal diferensiasi osteoblastik sehingga terjadi peningkatan gen penanda osteogenik seperti Alkaline Phosphatase (ALP), osteocalsin, Bone Morphogentic Protein-2 (BMP-2), RUNX-2, Col. 1 dan OPN.

Kata kunci : *fucoidan, brown seaweed, osteoblas, bone tissue engineering, alveolar bone loss*

EFFECTIVENESS OF FUCOIDAN IN STIMULATING OSTEOBLAST CELLS IN BONE REGENERATION

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ABSTRACT

Background: There are several cases related to bone destruction in the oral cavity, such as complications from tooth extraction and periodontitis leading to alveolar bone loss. Tissue engineering can restore and repair a lost or damaged network function. One biomaterial that plays a role in bone regeneration is fucoidan from brown algae marine biopolymer, which contains biomaterials that can make new osteoblast cells. **Purpose**: In general, this literature review aims to find out that fucoidan can be used to stimulate the growth of osteoblast cells in bone regeneration. **Result**: From the journals that have been reviewed, it was found that fucoidan is helpful as a functional food and is a drug for osteoporosis, preventing bone loss, promoting bone formation in vitro and in vivo, as well as inhibiting excessive bone resorption. **Conclusion:** This review has shown that fucoidan is known to have biological activities such as anticoagulant and antithrombotic, antioxidant and acts as a phenotypic marker in the early stages of osteoblastic differentiation resulting in an increase in osteogenic marker genes such as Alkaline Phosphatase (ALP), osteocalcin, Bone Morphogenetic Protein-2 (BMP). -2) RUNX-2, Col. 1, and OPN.

Keywords: *fucoidan, brown seaweed, osteoblas, bone tissue engineering, alveolar bone loss*

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CHAPTER I

INTRODUCTION

1.1 Background

In the sector of dentistry, bones can be damaged or lost due to trauma, tumors, or infections, causing essential organs to be unprotected from external impacts, loss of bone mobility, and increased muscle load[1]. Several cases are related to bone destruction in the oral cavity, such as complications due to tooth extraction and periodontitis, which leads to alveolar bone loss.

Complications due to tooth extraction are a condition of procedure failure that occurs without planning, has various causes and consequences. One of them is caused by excessive or poorly controlled pressure when the tooth is extracted and is not given further treatment. In addition, complications can occur based on local and systemic factors of the patient. In this case, the movement of the jaw becomes difficult and disturbed so that the gingiva that is rarely used tends to thin and affects the condition of the teeth.[2] Alveolar bone loss is known for imbalances and bone loss due to osteoporosis, cancer, and inflammatory diseases such as periodontitis[3,4].

The following case of bone damage and the most common in the oral cavity is periodontitis. This disease is an inflammation of the gingiva that has reached the periodontal ligament due to excessive plaque accumulation so that alveolar bone loss can occur and lead to tooth mobility and detachment from the socket[5,6]. The number of periodontitis cases in Indonesian society refers to the 2018 Basic Health Research Results Report (RISKESDAS); the prevalence of periodontitis at the age of 15-24 years is 67.8%, and the most are in the 45-54 year age range of 77.8%[7,8].

The standard therapy in cases of bone damage in the oral cavity is Bone Graft, which is divided into three types, namely Autograft, Allograft, and Xenograft. The type of Bone Graft is based on the origin of the bone used, as in Autograft using the patient's bone; Allograft uses bone from another patient of the same species, while Xenograft uses bone from a different species such as animal bone. Bone grafts must have osteogenesis, osteoinduction, and osteoconduction properties for bone regeneration. However, this therapy has several clinical demands, rarely used[9].

Technology growing in medicine is one of them in tissue engineering that aims to restore and repair the function of lost or damaged tissue. Scaffold, stem cells, and growth factors as biomaterials used in tissue engineering cannot be separated, then combined, and results match the natural regeneration of cells, tissues, and organs. Tissue engineering has become a more frequently used therapy in recent years because it uses natural or synthetic materials or a combination of both so that it is more biocompatible for growth and better cell attachment[10,11]. One biomaterials that play a role in the bone regeneration process is Fucoidan from brown algae marine biopolymer, which contains biomaterials that can make new osteoblast cells.

Fucoidan contains a substantial presentation of the L-Fucose group, and sulfate ester is a sulfated polysaccharide that has biological activity as anti-coagulant, anti-inflammatory, anti-cancer. It can contribute to osteogenesis by influencing osteoblast cells to form and regenerate bone tissue. Osteoblast cells are bone cells that play an essential role in bone deposition and maintain bone dynamics.

Fucoidan affects the growth of osteoblasts characterized by an increase in Alkaline Phosphatase (ALP), osteocalcin, and Bone Morphogenetic Protein-2 (BMP-2)[12].

Fucoidan, in the research results of Lu et al. (2019), was reported to be able to increase ALP and stimulate the proliferation of mesenchymal stem cells resulting in osteoblastic activity (increased osteoblast cells and mineral count were found). ALP is an enzyme that plays a role in bone formation. In addition, fucoidan has also been shown to suppress the osteoclast process in bone and increase osteoblast cells by stimulating ALP and BMP-2 in the study of Venkatesan et al. (2014) combined with chitosan extract.

However, the use of fucoidan is still not effective because the public does not know widely the potential techniques for extracting and processing these biomaterials. Therefore, the authors are interested in conducting a study entitled "Effectiveness of fucoidan in stimulating osteoblast cells in bone regeneration" through a literature review

1.2 Problem Statement

1. Can fucoidan stimulate the growth of osteoblast cells in bone regeneration?
2. What is the active substance of fucoidan that can stimulate the growth of osteoblast cells in bone regeneration?

1.3 The objective of the research

1. Untuk mengetahui pemanfaatan fucoidan dalam merangsang pertumbuhan sel-sel osteoblas pada regenerasi tulang
2. Untuk mengetahui zat aktif dari fucoidan yang dapat merangsang pertumbuhan sel-sel osteoblas pada regenerasi tulang

1.4 The significance of the research

1. For the public, to provide an understanding of the effectiveness of fucoidan in stimulating the growth of osteoblast cells in bone regeneration
2. For science, which can increase knowledge and become one of the reading materials for dentistry regarding the effectiveness of fucoidan in stimulating the growth of osteoblasts in bone regeneration
3. For the author, to add insight regarding the effectiveness of fucoidan

CHAPTER II

LITERATURE REVIEW

2.1 Bone

Bone is a tissue that differs from other connective tissue in that it consists of cells and ground substances that function as a support and protective framework for the skeleton. Bone has two main functions, namely as support for structural organs as well as a place for calcium metabolism. Bone is a tissue that has a complex system of cell regeneration, where old cells are remodeled and then replaced with new cells. Osteoblasts together with osteoclasts become cells that each work in the process of bone formation and resorption. Excessive osteoclast activity is the cause of the loss of bone substance[4,13].

2.1.1 Bone cells

Bone consists of cell components such as osteoprogenitors, osteoblasts, osteocytes, and osteoclasts.

1. Osteoprogenitor

   Osteoprogenitor, also known as Osteogenic, plays a role in dividing into osteoblast cells and osteoclast cells. Osteoprogenitor cells are derived from mesenchymal tissue, which becomes the most active cells during growth and when bone fracture recovery can be reactivated[14].

2. Osteoblast

The cells that play a role in forming new bone are osteoblasts. Osteoblast cells make up 4-6% of all bone cells found along the bone surface. Osteoblasts are a product of mitosis from osteoprogenitor cells, mesenchymal stem cells (MSCs) originating from the bone marrow. These cells synthesize the protein Collagen type I and regulate mineralization. Osteoblasts may become bone lining cells, osteocytes cells, or undergo apoptosis[15].

Through matrix vesicles, osteoblasts also promote mineralization of organic matrix, extracellular organics (found in osteoids), and those associated with matrix calcification. Alkaline phosphatase (ALP), Adenosine triphosphatase (ATP), inorganic pyrophosphatase, and Proteinase (plasminogen activator) contained matrix vesicles, which through a local enzymatic accumulation of calcium and phosphate, serve to form hydroxyapatite crystals[16].

3. Osteocytes

Osteocytes are the longest-lived cells and the most abundant total bone cells. Osteocyte cells are also derived from osteoblast differentiation from mesenchymal stem cells (MSCs). Osteocytes are actively trapped in lacunae which are surrounded by a mineralized bone matrix during the process of bone formation. Osteocytes play a role in bone remodeling regulating osteoclasts and osteoblast differentiation[14].

4. Osteoclasts

In addition to Osteoblast cells, osteoprogenitors also undergo mitosis to become osteoclast cells. Osteoclasts are known to be the only cell that can resorb bone. Found only in the calcified matrix, bone marrow is believed to be the site of osteoclast formation. Two cytokines are essential in forming osteoclasts, namely receptor activator of nuclear kappa B Ligand (RANKL) and macrophage colony-stimulating factor (M-CSF)[16,17].

2.2 Cases of bone damage in the oral cavity

Pathological bone damage caused by local or systemic factors is a loss of bone structure. Several cases of bone damage are known in the sector of Dentistry such as bone complications after tooth extraction, Periodontitis and Alveolar Bone Loss.

2.2.1 Bone complication after tooth extraction

Tooth extraction is a minor surgical procedure (mild surgery) that involves hard and soft tissues in the oral cavity in dentistry by removing intact teeth or root remnants or teeth that cannot be treated without causing pain and trauma. Before performing a tooth extraction, it is necessary to pay attention to the patient's general condition and ensure that he is in good

health to reduce the risk of complications[18]. According to Pederson (1996), complications of tooth extraction are divided into three, namely intraoperative complications or during tooth extraction (fracture, displacement, bleeding, soft tissue injury), complications immediately after tooth extraction (bleeding, pain, allergic reaction to medication, edema) and complications long after tooth extraction (infection, dry socket or alveolitis)[2].

Some of the complications that can occur during tooth extraction is a crown fracture, root fracture, neighboring or antagonistic tooth fracture, restoration, fracture of the alveolar process to fracture of the mandible. The possibility of this complication can be prevented if the dentist performs an ideal tooth extraction procedure with the proper technique to overcome the difficulties of the procedure[19].

2.2.2 Periodontitis

Periodontitis is an inflammation in the periodontium caused by gram-negative anaerobic bacteria Aggregatibacter actynomi-cetemcommitans, Porphyromonas gingivalis, and Prevotella intermedia.[15] This disease begins with gingival inflammation (gingivitis) at the marginal gingiva but does not reach the periodontal ligament due to excessive plaque accumulation, whereas inflammatory periodontitis already involves the periodontal ligament[21,22]. This situation occurs because there is no treatment

when gingivitis progresses. Based on the American Academy of Periodontology, periodontitis is classified based on the condition into two, namely chronic periodontitis and aggressive periodontitis[23].

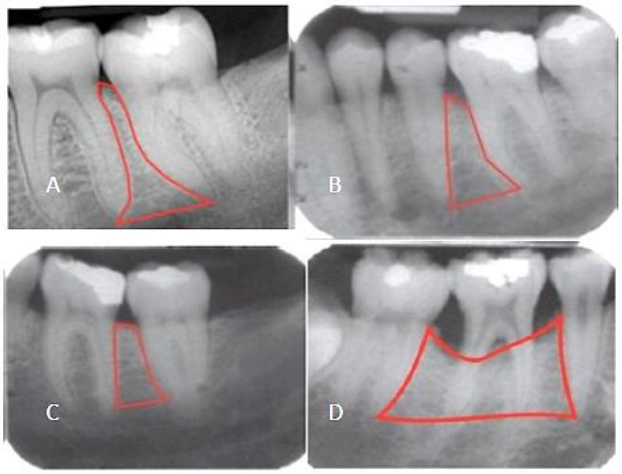

Figure 2.1 Alveolar bone radiography in: (a) normal; (b,c) chronic periodontitis; (d) aggressive periodontitis (Source: Rahmania., et al. 2019)

Periodontitis Chronic periodontitis is the most common disease in adults and occurs in children. This disease has a slow to moderate progression so that the symptoms that appear when around the age of 40 years, such as supragingival and subgingival plaque, gingival swelling and redness, changes in gingival margins (crappy papillae, recession), loss of gingival stippling, formation of pocket, causing bleeding on probing, bone loss and loss of tooth mobility. Chronic periodontitis is classified according to attachment loss into:

a. Localized chronic periodontitis, bone attachment, and loss of less than 30% of teeth

b. Generalized chronic periodontitis, bone attachment, and loss of more than 30% of teeth

The etiology of chronic periodontitis can be prevented, like smoking and diet, and those that cannot be changed, such as genetic disorders and metabolic disorders[20].

Aggressive periodontitis was only named when 1999 changed terminology over the years, initially named diffuse atrophy of the alveolar bone in 1923. Aggressive periodontitis is early-onset and rapidly progressive. Patients with this disease may complain of bad breath (halitosis), discharge of pus from the gums, and food impaction due to loss of contact points between teeth.[24] Aggressive periodontitis is also divided into localized aggressive periodontitis (LAP) and generalized aggressive periodontitis (GAP) based on history, clinical data, and radiographic. Patients with localized aggressive periodontitis are usually younger than patients with generalized aggressive periodontitis because systemic antibody titers of GAP are more pronounced against periodontal pathogens. GAP is a periodontal disease with the highest severity characterized by acute inflammation, bleeding that occurs spontaneously or with little stimulation, ulceration, and clinical appearance is mild but has deep pockets when demonstrated on probing[20].

2.2.3 Alveolar Bone Loss

Alveolar bone mechanically undergoes a continuous remodeling cycle, which degrades the bone mineral matrix in which Osteoclasts are activated and attach to the bone surface and then produces H+ protons and proteases and Osteoblasts synthesize Osteoid and then regulate the mineralization process. Alveolar bone volume is stable due to the process of regeneration and balanced bone formation, so that old bone is replaced into the new bone through the regulation of various hormones and cytokines[25].

One of the diseases in the oral cavity, such as Periodontitis, found an imbalance of alveolar bone remodeling, the formation of periodontal pockets caused by the virulence of periodontal pathogens that penetrate the oral mucosal defenses, and then force the epithelium to retreat apically on the root surface. Inflammatory cells such as neutrophils, macrophages, and T/B cells are released from Resident Cells (cells that remain in tissue, fibroblasts), which produce antimicrobial agents and enzymes to eliminate pathogens but gradually penetrate deeper into the periodontal tissue to the alveolar bone, which can cause inflammation, so the bone remodeling process to be disrupted[25].

2.3 Bone Remodeling

Active bone remodeling is the process of bone loss by osteoclast cells and then forming new bone by osteoblast cells. It aims to maintain bone strength as well as mineral homeostasis. Bone resorption and formation are closely related to bone remodeling, which makes the volume and structure of the bone unchanged[26]. Anatomically, the remodeling cycle occurs in the Basic Multicellular Unit (BMU), which contains osteoclasts, osteoblasts, and capillaries. It has a longer lifespan than osteoblasts and osteoclasts due to BMU requiring these cells constantly, which is regulated by osteocytes[14].

The remodeling cycle that occurs successively from birth to death is the activation phase, the bone resorption phase, the reversal phase, the bone formation phase, and the termination phase[15,21.] The first stage of the remodeling begins by detecting signals in the form of direct mechanical strain on the bone that damages bone cell hormones (estrogen and PTH) and structural ones that make the response to homeostatic changes more systemic. PTH is a hormone produced by the secretion of the parathyroid glands that can maintain calcium homeostasis; on the surface of osteoblasts, this hormone activates receptors such as the seven-transmembrane G-protein-coupled receptor and the PTH receptor, which triggers a transcriptional response to produce the secretion of osteoclast precursor molecules. RANKL (Receptor Activator of Nuclear B Ligand) and its receptor RANK (Receptor Activator of Nuclear B) affect osteoclasts' activity and differentiation and initiate the next phase, the next bone resorption phase[21,22].

Osteoclasts only take about 2 to 4 weeks to enter the bone resorption phase. In response to PTH, osteoblast expression of major osteoclastogenesis cytokines such as CSF-1 (The colony stimulating factor-1) or also known as M-CSF, RANK, and osteoprotegerin (OPG) is modulated. CSF-1 works together with RANK to promote the proliferation and differentiation of osteoclast precursors into multinucleated osteoclasts, directing cytoskeletal spread in mature cells, increasing resorption activity. Osteoclast formation is triggered by decreased expression of OPG and increased production of CSF-1 and RANK[21]. Osteoclasts regulate differentiation and activation of osteoclasts that attach to the bone surface and begin to dissolve bone after differentiation. Osteoclasts will experience apoptosis if they have acidified the bone matrix to dissolve inorganic components, releasing lysosomal enzymes, namely Cathepsin K and MMP9, which work to degrade organic bone components. This phase ends with osteoclast apoptosis in order to avoid excessive bone resorption[22].

The reversal phase receives a coupling signal that makes a reversal phase transition from the resorption phase to the bone formation phase, which lasts about 4 to 5 weeks in the BMU[15,21].In this phase, the bone surface is prepared to deposition a new bone matrix by removing the unmineralized collagen matrix by osteoblastic derived cells[15]. Cells that act like macrophage cells can remove debris resulting from matrix degradation[22].

Osteocytes provide mechanical stimulation and the endocrine signaling PTH which can induce bone growth signals. Osteoblasts synthesize and

secrete Type-1 collagen-rich osteoid matrix and regulate osteoid mineralization in the Formation Phase, which lasts approximately four months[20]. Progenitors of differentiation osteoblasts secrete molecules that form replacement bone after returning to resorption lacunae[21]. Good remodeling if there is a balance between the resorption phase and the bone formation phase; if this is not found, it will affect bone mass until it ends in a pathological direction[22].

The end of the remodeling cycle is when the replaced bone has been wholly reabsorbed. Osteoblasts undergo apoptosis after mineralization and then turn into bone lining cells or are buried in the bone matrix and then differentiate into osteocytes which hold the key as a sign of the end of the remodeling stage. When the remodeling process begins again, the resting bone surface is rebuilt and continues[15,21].

2.4 Fucoidan

Fucoidan is a polysaccharide of the L-Fucose group, and the sulfate ester contains a substantial percentage that can be found in Brown Algae. It has many biological activities such as anticoagulant and antithrombotic, antiviral, antitumor and immunomodulatory, anti-inflammatory, blood lipid reducing, antioxidant and anticomplementary, activity against hepatopathy, uropathy and kidney, gastric protective effect, and therapeutic potential in surgery.

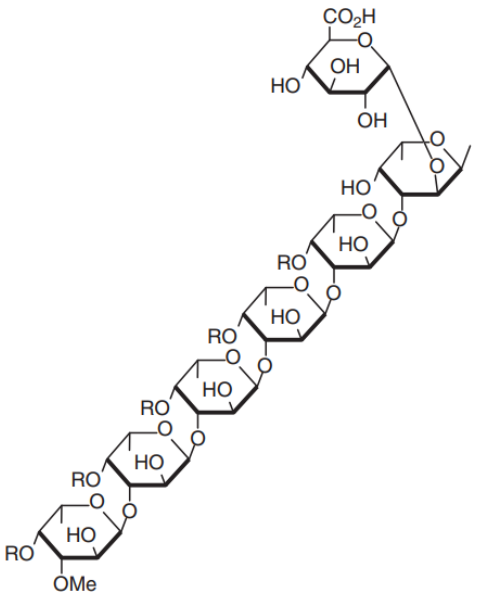

Figure 2.2 Chemical structure of fucoidan (Source: Chandika P and Jung W. 2015)

Each species of agae has fucoidan which has a different structure, but there is always a backbone from fucan sulfate, which contains other monosaccharides (mannose, galactose, glucose, xylose) and uronic acid, to acetyl groups and proteins.[12].

According to IUPAC rules, this polysaccharide is now known as "Fucoidan" and can also be called fucan, fucosan, and fucan sulfate, which in 1913 was named "Fucoidin" by Kylin, who isolated it for the first time from brown algae. Fucoidan content is confirmed to have been found in various algae such as Fucus vesiculosus, Sargassum stenophyllous, Chorda phylum, Ascophyllum nodosum, Dictyota menstrual, Fucus evanescens, Fucus serratus, Fucus distichus, Caulerpa racemosa, Hizikia fusiform, Craslipussifolia, Analipus japonicus and Laminaria hyperborean with different extraction methods[27]. Fucoidan has been studied more than other polysaccharides in recent

years because it is easily found in cheap sources to develop drugs or functional foods fungsional[12].

Figure 2.3 Algae that contain fucoidan. 1. *Fucus vesiculosus*, 2. *Laminaria digitata*, 3. *Fucus evanescens*, 4. *Fucus serratus*, 5. *Ascophyllum nodosum*, 6. *Pelvetia canaliculata*, 7. *Cladosiphon okamuranus*, 8. *Sargassum fusiforme*, 9. *Laminaria japonica*, 10. *Sargassum horneri*, 11. *Nemacystus decipiens*, 12. *Padina gymnospora*, 13. *Laminaria hyperborean* (Sumber: Luthuli S., et al. 2019)

There are various methods of extracting fucoidan from algae, such as enzymatic extraction, microwave-assisted extraction, ultrasound-assisted extraction, pressurized liquid extraction, subcritical water extraction, and the most widely used technique is isolating fucoidan from macroalgae through ethanol precipitation. The beginning of isolating fucoidan by grinding dry matter to obtain micrometer-sized particles, followed by removing pigment and dust particles by adding a sufficient amount of ethanol. Then, the algae were washed using acetone and centrifuged, and then dried. Algae in the range of 5g are deposited with distilled water and stirred for one hour; the process can be repeated two to three times to obtain maximum fucoidan extract results. The supernatant was treated using 1% CaCl2 solution and stored overnight at 4oC[27].

Fucoidan was investigated to act as a phenotypic marker in the early stages of osteoblastic differentiation by increasing alkaline phosphate (ALP) and osteocalcin levels and interested in bone formation remodeling mineralization from its positive effect on bone morphogenic protein-2 (BMP-2). By osteoblasts, osteocalcin is tasked with marking specific cell proteins for differentiation of selected osteoblast terminal cells into cell culture media[28].

2.5 Bone therapy in bone repair

Bone graft is a treatment with a surgical procedure performed to repair bone damage, using materials from the patient's own body (autograft), synthetic or natural materials to replace lost bone. The material from the bone graft must meet the requirements of bone regeneration mechanisms such as osteoconduction, osteoinduction, and osteogenesis. Osteoconduction is a condition when providing bone graft material that functions as a scaffold for new bone growth; Osteoinduction is a condition where osteoprogenitor cells are stimulated to differentiate into osteoblasts, producing new bone; Osteogenesis is a condition for growth and bone formation by osteoblasts derived from bone graft material. The bone graft material acts as a scaffold for existing osteoblasts; if it is osteoconductive and osteoinductive, it can trigger the growth of new osteoblasts and promote faster graft integration[10].

In addition to playing a role in bone remodeling, a bone graft can also stimulate the formation of cementum and periodontal ligament and has a skeletal

structure for blood clotting. However, deficiencies were found that allow the risk of a longer recovery, more significant donor morbidity, infection, and weak osteoinductivity. Therefore, current bone grafts have shortcomings in terms of safety and alternative materials and techniques[29,30].

Currently, there is a qualified technology in the medical sector that focuses on encouraging regeneration or regrowth of damaged tissue, namely tissue engineering that using factors (Scaffold, Stem Cells, and Growth factors)[10,31]. Cells, extracellular matrix, intercellular communication, inter-matrix communication and growth factors are also needed from a biological perspective[32]. There are also crucial holders in bone tissue engineering such as:

1. Scaffold, must be very similar to the natural bone extracellular matrix
2. Osteogenic cells, placed in the bone matrix
3. Morphogenic signal, phonetically guides the cell to the desired type
4. Vaskularization sufficient, so that the nutritional needs of growing tissues are met[32].

All these components must be combined to get the desired result in a coordinated time. Bone has a 3D configuration that cells cannot do in 3D in vitro. Therefore a scaffold is needed to resemble the structure and function of the natural extracellular matrix of bone[33].

Scaffolds or from biomaterials have an important role in reconstructing bones divided into two, namely synthetic and natural biomaterials. Synthetic biomaterials are available polymers whose structure and chemical properties are

known to be biodegradable, such as poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(3-caprolactone) (PCL), polylactide (PLA), polyglycolide (PGA). , and poly(lactide-glycolide) acid (PLGA)]. While the natural biomaterials most often used for scaffold fabrication are collagen (type I, II, III), as well as other natural polymers (gelatin, alginate, fucoidan, chitosan, starch, cellulose materials[34,35].

Providing chemical stability in terms of cell compatibility, adhesion performance, cell proliferation in surrounding tissues, in vivo and in vitro proliferation is the goal of the ideal scaffold. Scaffold biomaterials, of which various types have been investigated, can support cell attachment and engineer tissue to new organs[10]. The nature of the scaffold in bone tissue engineering is that when osteoblasts differentiate, they are also able to secrete their cellular matrix together with the degraded scaffold, have suitable porosity and osteoinduction, and are osteoconductive, biodegradable and biocompatible[31,32].