Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Feb 02; 11(F):81-85.
https://doi.org/10.3889/oamjms.2023.11210
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

Effectiveness of Marine Bioactive Compound Fucoidan in Stimulating Osteoblast Cells Formation: A Systematic Review

Nurlindah Hamrun[1]*, Daranisa Wulan Purnamasari[1], Andi Sitti Hajrah Yusuf[2], Muhammad Ruslin[2]

[1]Department of Oral Biology, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia; [2]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia

Edited by: Eli Djulejic
Citation: Hamrun N, Purnamasari DW, Yusuf ASH, Ruslin M. Effectiveness of Marine Bioactive Compound Fucoidan in Stimulating Osteoblast Cells Formation: A Systematic Review. Open Access Maced J Med Sci. 2023 Feb 02; 11(F):81-85. https://doi.org/10.3889/oamjms.2023.11210
Keywords: Fucoidan; Brown seaweed; Osteoblast; Tissue engineering; Alveolar bone
***Correspondence:** Dr. Nurlindah Hamrun, Department of Oral Biology, Faculty of Dentistry, Hasanuddin University, Makassar 90245, Indonesia.
E-mail: lindahamrun@unhas.ac.id
Received: 02-Nov-2022
Revised: 12-Jan-2023
Accepted: 30-Jan-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Bone loss in the oral cavity can occur in various situations, including periodontitis-related issues and complications after tooth extraction. A damaged or lost alveolar bone can be restored through a tissue engineering approach. Fucoidan, a marine biopolymer derived from brown algae, is one biomaterial that aids bone regeneration since it contains biomaterials that can generate new osteoblast cells.

AIM: The purpose of this review is to determine whether fucoidan can be employed to promote osteoblast cell growth during bone repair.

METHODS: The search strategy was performed in PubMed; Elsevier (Scopus); ScienceDirect; Libgen, and Google Scholar. In addition, a manual hand searching was performed to locate and identify additional studies.

RESULTS: Based on the reviewed articles, it has been discovered that five met the inclusion criteria and found that the marine bioactive compound fucoidan can significantly increase the expression of ALP activity.

CONCLUSION: Fucoidan is considered to have biological properties, including antithrombotic, anticoagulant, and antioxidant. It also serves as a phenotypic marker during the early stages of osteoblastic differentiation.

Introduction

Bone is a tissue that has a complex system of cell regeneration, where old cells are remodeled and then replaced with new cells [1], [2], [3]. Together, osteoblasts and osteoclasts comprise cells that are involved in both the formation and resorption of bone. The loss of bone material is spurred on by excessive osteoclast activity [1], [2], [3], [4]. In dentistry, bone can be lost or destroyed due to trauma, tumors, or infections, leaving vital organs vulnerable to injury [5].

Bone grafting, which comes in three types (Autograft, Allograft, and Xenograft), is the usual treatment for cases of bone loss in the oral cavity [5], [6], [7]. The type of bone graft depends on where the bone came from; for example, an autograft is obtained from the patient's bone, an allograft uses the bone of the same species, and a xenograft uses bone from an entirely other species, such as an animal bone [5], [7], [8]. For bone regeneration, bone transplants must possess osteogenesis, osteoinduction, and osteoconduction characteristics [5]. However, flaws were discovered that increase the likelihood of a protracted recovery, considerable donor morbidity, infection, and poor osteoinductivity [6], [9]. Therefore, there are issues with the safety of present bone grafts [7]. Due to this fact, it is crucial to find alternative materials and techniques to treat alveolar bone loss [6], [9].

Fucoidan, a marine biopolymer derived from brown algae, which contains biomaterials capable of producing new osteoblast cells, is one biomaterial that contributes to bone regeneration [10], [11]. Fucoidan includes a substantial presentation of the L-Fucose group, and sulfate ester is a sulfated polysaccharide with biological activity as an anti-coagulant, anti-inflammatory, and anti-cancer [10], [12]. It can contribute to osteogenesis by influencing osteoblast cells to form and regenerate bone tissue [11], [12]. Osteoblast cells are bone cells that play an essential role in bone deposition and maintain bone dynamics [3], [13]. To date, the use of fucoidan is still ineffective and more people need to be educated about the potential methods for extracting and processing these biomaterials. Given this context, the authors are keen to conduct a study to determine whether fucoidan can be used to promote osteoblast cell formations during bone regeneration.

Methods

Search strategy

This systematic review was conducted following preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Information sources

A structured search of the following critical electronic databases served as the primary source of literature: PubMed, Elsevier (Scopus), ScienceDirect, Libgen, and Google Scholar. Hand-searching the reference lists of included studies or other pertinent publications will be the secondary source of potentially relevant information.

The electronic search was performed using the combination of the following phrases: fucoidan, brown seaweed, osteoblas, bone tissue engineering, and alveolar bone loss.

Eligibility criteria

Studies were chosen based on the following inclusion criteria: (1) Original paper; (2) published during the past 10 years (2011–2021); (3) written in the English language; and (4) accessible full-text.

Studies were disqualified if they were either (1) abstract-only, closed-access, or (2) literature review articles.

Selections of study

The studies will be assessed following the qualifying requirements and the selection procedure will be separated into two stages. Transferring references to an online reference management solution will handle data (EndNote X9.2 reference manager). The management tools will be used to record the selection process. As the first step, duplicates of the first search results will be removed. Eligible full texts will be examined after comparison and agreement with the first screening procedure. The study will be disregarded if no full text is located. The PRISMA design specifies that a flow diagram will be used to follow the process (Figure 1).

Extraction of data

The following information was taken from each included study under the proposed standard form: author's name, country, species, sample location, extraction method, bioactive compound, cell lines, evaluation observation, and result.

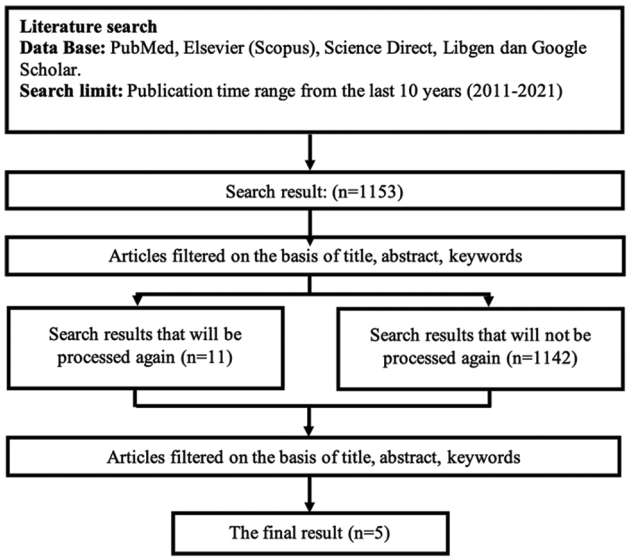

Figure 1: Flow of study selection process

Results

The literature search results through PubMed, Elsevier (Scopus), Science Direct, Libgen, and Google Scholar websites were conducted from November 01, 2021 to January 14, 2022, using pre-defined keywords and yielded a total of 1153 articles from the electronic databases. Only 11 studies were identified as eligible after removing duplicates and screening titles and abstracts. Following the evaluation of full-text articles from 11 studies, five met the inclusion criteria and were included in the final quality assessment, as shown in Figure 1.

The study characteristics are summarized in Table 1. The first study was conducted by Hwang *et al*., 2016, which evaluated the *in vitro* and *in vivo* effects of low molecular weight (LMW) fucoidan on the osteogenic differentiation properties of bone [14]. This study used fucoidan extract from the algae *Sargassum hemiphyllum*. It then hydrolyzed with glycolytic enzymes to produce fucoidan LMW (<1 kDa) to determine the effect on proliferation and differentiation using the 7F2 osteoblastic cell line *in vitro*. ALP activity test and osteocalcin (OC) secretion as a phenotypic marker of increased osteoblast differentiation were carried out by inoculation of 7F2 cells (1 × 105) treated with 10 μL of different concentrations (0 [control], 0.25, 0.5, 1, and 2 mg/mL) of fucoidan and LMW for 48 h on medium. They reported that there was a significant increase in the concentration of fucoidan LMW 0.25–2 mg/mL, and ALP activity increased to 135.35 ± 2.91% at 2 mg/mL when compared to the control group.

The second literature was conducted by Park *et al*. in 2012 regarding the sulfated polysaccharide fucoidan capable of stimulating the differentiation of human adipose-derived stem cells (hADSCs) into osteoblasts through matrix deposition analysis and expression of osteogenic marker genes [15]. In this

Table 1: Characteristic of included studies

Author (year)/country	Species	Subject of study	Object of study	Results
Hwang *et al*., (2016)/Taiwan [14]	*Sargassum hemiphyllum*	LMW fucoidan on osteogenic differentiation of bone	ALP activity and osteocalcin secretion	ALP activity increased to 135.35±2.91% at 2 mg/mL fucoidan and increased osteocalcin secretion at concentrations from 0.5 to 2 mg/mL by 7F2 cells cultured with LMW fucoidan.
Park *et al*. (2012)/Korea [15]	Sulfated polysaccharide fucoidan	Fucoidan stimulates the differentiation of hADSCs into osteoblasts	Comparison of hADSC cultured with and without fucoidan in osteogenic media	hADSC cells cultured with fucoidan in osteogenic media were highly positive compared without fucoidan.
Kim *et al*. (2018)/Korea [16]	*Laminaria japonica*	Fucoidan induces osteogenic differentiation	MSCs were cultured and treated with fucoidan	The highest ALP activity after treatment with 1 g/mL fucoidan.
Kim *et al*. (2015)/Korea [17]	*Laminaria japonica*	Effect of fucoidan on osteoblast differentiation	hABM-MSC	The ALP staining test showed that fucoidan significantly induced ALP activity in the range of 0.1–1.0 g/mL−1; and Real-time PCR test results reported that the mRNA expression level of osteoblast marker genes increased after treatment with 1 μg/mL fucoidan.
Hsu *et al*. (2021)/Taiwan [18]	*Sargassum horneri*	Hyaluronan and fucoidan crosses in inducing osteoblast differentiation for the manufacture of composite hydrogels	ALP activity test	The results of the ALP activity test showed that fucoidan was able to increase ALP activity as a phenotypic marker for early-stage osteoblast differentiation of MG63 cells.

LMW: Low molecular weight, hADSCs: human adipose-derived stem cells, MSCs: Mesenchymal stem cells, hABM-MSC: Human alveolar bone marrow-derived mesenchymal stem cells.

study, fucoidan with high molecular weight (HMW) (>30 kDa) was dissolved in dimethyl sulfoxide (DMSO, 10 mg/mL), then filtered using a 0.2 mm filter, then stored at −20°C. Their results showed that hADSCs cultured with fucoidan in osteogenic media (OS + Fuco) were very positive compared without fucoidan in the ALP, ARS, and VK staining assays so that fucoidan significantly induced osteogenic differentiation. However, it did not show a specific reaction in any staining test when cultured in Dulbecco's modified Eagle's medium (DMEM) with fucoidan (ADSC + Fuco).

The third study was conducted by Kim *et al*. in 2018 regarding fucoidan-induced osteogenic differentiation that promotes angiogenesis by inducing vascular endothelial growth factor secretion and accelerating bone repair [16]. This study uses fucoidan extracted from brown algae Laminaria with molecular weights ranging from 3.3 to 100 kDa and mesenchymal stem cells (MSC) from alveolar bone marrow cultured in DMEM in a CO_2 incubator humidified at 37°C. The results showed that fucoidan in concentrations of 1 and 5 g/mL significantly increased the MSC proliferation compared to untreated control cells. In a quantitative direct-time PCR assay lasting 5 days of fucoidan treatment, it was reported that the mRNA levels of osteoblast marker genes such as RUNX2, ALP, OC, bone morphogenetic protein-2 (BMP-2), and collagen Type 1 (Col-1) increased significantly.

The fourth literature by Kim *et al*.; 2015, evaluated fucoidan's ability to differentiate osteoblasts through BMP2-Smad 1/5/8 dependent on c-Jun N-terminal Kinase and ERK in human MSC signaling [17]. This study used human alveolar bone marrow-derived MSC to determine the effect of fucoidan on osteoblast differentiation. The results of the ALP staining test showed that fucoidan significantly induced ALP activity in the range of 0.1–1.0 μg/mL. Real-time PCR test results reported that the mRNA expression level of osteoblast marker genes (RUNX2, Col. 1, OC, and ALP) increased significantly after the treatment with 1 μg/mL fucoidan.

The fifth study conducted by Hsu *et al*., 2021 explained the assay of crosses of hyaluronan (HA) and fucoidan in inducing osteoblast differentiation for the manufacture of composite hydrogels [18]. This study evaluated the effects of methacrylate-HA and methacrylate-fucoidan on the mechanical properties of hydrogels, cell proliferation, cell adhesion, and production of ALP. The results of the ALP activity test for 3 days showed that fucoidan could increase ALP activity as a phenotypic marker for early-stage osteoblast differentiation of MG63 cells. This study suggests that fucoidan can be used as a potential candidate to form a biocomposite scaffold in bone tissue engineering because it allows the adhering cells to differentiate and mineralize.

Discussion

Bone is a connective tissue responsible for supporting structural organs and protecting the skeleton. Another function of bone is as a place of calcium metabolism [3], [19], [20]. In dentistry, alveolar bone is found in the upper jaw (maxilla) and lower jaw (mandible). Alveolar bone plays a role as the main supporting structure of the teeth, maintains mineral homeostasis, and has an endocrine function [5]. To maintain bone strength and mineral homeostasis, bone actively performs bone remodeling, replacing or reshuffling old bone by resorbing bone and then replacing it with new bone to prevent bone accumulation with microdamage [19], [20], [21]. The bone remodeling process involves two central cells, osteoblasts that play a role in bone deposition and osteoclasts that carry out bone resorption. However, if osteoclasts experience excessive bone resorption, it will disrupt the bone remodeling process, resulting in bone loss [19], [20].

Tissue engineering has become a bone repair therapy that is more often used in recent years because it uses natural or synthetic materials or a

combination of both [22], [23]. It is more biocompatible for growth and better cell attachment [8], [23]. Several studies have found that brown algae mucus matrix or interstitial tissue contains a polysaccharide of the L-Fucose group and a sulfate ester (soluble in sulfated heteropolysaccharide) named fucoidan, which is known to treat bone defects (especially in MSC) by promoting osteoblast differentiation so that an increase in ALP, OC, and BMP-2 [22], [24]. ALP functions to increase the local concentration of inorganic phosphate, reduce the concentration of extracellular pyrophosphate, inhibit mineral formation, and act as a promoter of mineralization to become an essential component in bone formation. OC is a bone crystal growth regulator associated with its high affinity for hydroxyapatite crystals, making it a crucial part of bone minerals [21]. Fucoidan consists of very complex compositions such as galactose, rhamnose, xylose, mannose, uronic acid, and especially fucose and sulfuric acid, making the structure of the pure compound known. However, the overall structure still needs to be clarified [22].

Fucoidan has a sulfate region to inhibit bone marrow macrophage osteoclastogenesis by inhibiting RANK-induced MAPK activation through the downregulation of genes involved in osteoclast differentiation and resorption [24]. Fucoidan has been shown to interact directly with various growth factors, such as BMPs, and stimulate fibroblast proliferation. It is known that fucoidan can also induce the differentiation of collagen fibrillation and human osteoblast cells [25]. The LMW has more potent bioactivity than HMW fucoidan; in the study of Zhang *et al*. 2020, it was found that the LMW Fucoidan <30 kDa had a potential effect on the osteoconductive properties of bone biomaterials [26].

This polysaccharide has a strong osteogenic effect; according to the research of Chandika and Jung, after BMP-2 is secreted, a lot of ALP is produced. BMP-2 is a cytokine that promotes bone formation, induces osteoblast differentiation, and is an important marker of osteoblast activity and function [22]. ALP activity increased depending on the dose of fucoidan, and this study occurred when the fucoidan dose was 200 μg/mL. After a dose of 100 μg/mL, which lasted 6 days, RUNX2 and BMP2 gene expression were, respectively, 8.6-fold and 2.5-fold higher than the control group. Being the most critical transcriptional regulator in bone tissue, acting as an essential regulator in the production and maturation of osteoblasts is the role of RUNX2 [22].

Conclusion

Fucoidan can probably act as a phenotypic marker in the early stages of osteoblastic differentiation by increasing osteogenic marker genes such as ALP, OC, BMP-2, RUNX-2, Col-1, and OPN. The increase in the osteogenic marker gene depended on the dose of fucoidan treatment.

References

1. Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. J Immunol Res. 2015;2015:615486. https://doi.org/10.1155/2015/615486
   PMid:26065002
2. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of bone tissue: Structure, function, and factors that influence bone cells. Biomed Res Int. 2015;2015:421746. https://doi.org/10.1155/2015/421746
   PMid:26247020
3. Rucci N. Molecular biology of bone remodelling. Clin Cases Miner Bone Metab. 2008;5(1):49-56.
   PMid:22460846
4. Kenkre JS, Bassett J. The bone remodelling cycle. Ann Clin Biochem. 2018;55(3):308-27. https://doi.org/10.1177/0004563218759371
   PMid:29368538
5. Madanagopal TT, Agarwalla SV, Rosa V. Carbon nanocomposites for implant dentistry and bone tissue engineering. In: Applications of Nanocomposite Materials in Dentistry. Netherlands: Elsevier; 2019. p. 47-63.
6. Kumar P, Vinitha B, Fathima G. Bone grafts in dentistry. J Pharm Bioallied Sci. 2013;5(Suppl 1):S125-7. https://doi.org/10.4103/0975-7406.113312
   PMid:23946565
7. Amini AR, Laurencin CT, Nukavarapu SP. Bone tissue engineering: Recent advances and challenges. Crit Rev Biomed Eng. 2012;40(5):363-408. https://doi.org/10.1615/critrevbiomedeng.v40.i5.10
   PMid:23339648
8. Dhandayuthapani B, Yoshida Y, Maekawa T, Kumar DS. Polymeric scaffolds in tissue engineering application: A review. Int J Polym Sci. 2011;2011:290602. https://doi.org/10.1155/2011/290602
9. Saima S, Jan SM, Shah AF, Yousuf A, Batra M. Bone grafts and bone substitutes in dentistry. J Oral Res Rev. 2016;8(1):36-8. https://doi.org/10.4103/2249-4987.182488
10. Li B, Lu F, Wei X, Zhao R. Fucoidan: Structure and bioactivity. Molecules. 2008;13(8):1671-95. https://doi.org/10.3390/molecules13081671
11. Venkatesan J, Anil S, Rao S, Kim SK. Macroalgal fucoidan for biomedical applications. In: Handbook of Algal Technologies and Phytochemicals. Florida, United States: CRC Press; 2019. p. 13-23.
12. Luthuli S, Wu S, Cheng Y, Zheng X, Wu M, Tong H. Therapeutic effects of fucoidan: A review on recent studies. Mar Drugs. 2019;17(9):487. https://doi.org/10.3390/md17090487
    PMid:31438588
13. Huang X, Xie M, Xie Y, Mei F, Lu X, Li X, *et al*. The roles of osteocytes in alveolar bone destruction in periodontitis. J Transl Med. 2020;18(1):479. https://doi.org/10.1186/s12967-020-02664-7
    PMid:33308247
14. Hwang PA, Hung YL, Phan NN, Hieu BT, Chang PM, Li KL, *et al*. The *in vitro* and *in vivo* effects of the low molecular weight fucoidan on the bone osteogenic differentiation properties.

Cytotechnology. 2016;68(4):1349-59. https://doi.org/10.1007/s10616-015-9894-5
PMid:26271462

15. Park SJ, Lee KW, Lim, DS, Lee S. The sulfated polysaccharide fucoidan stimulates osteogenic differentiation of human adipose-derived stem cells. Stem Cells Dev. 2012;21(12):2204-11. https://doi.org/10.1089/scd.2011.0521
PMid:22050637
16. Kim BS, Yang SS, You HK, Shin HI, Lee J. Fucoidan-induced osteogenic differentiation promotes angiogenesis by inducing vascular endothelial growth factor secretion and accelerates bone repair. J Tissue Eng Regen Med 2018;12(3):e1311-24. https://doi.org/10.1002/term.2509
PMid:28714275
17. Kim BS, Kang HJ, Park JY, Lee J. Fucoidan promotes osteoblast differentiation via JNK-and ERK-dependent BMP2-Smad 1/5/8 signaling in human mesenchymal stem cells. Exp Mol Med 2015;47(1):e128. https://doi.org/10.1038/emm.2014.95
PMid:25572360
18. Hsu FY, Chen JJ, Sung WC, Hwang PA. Preparation of a fucoidan-grafted hyaluronan composite hydrogel for the induction of osteoblast differentiation in osteoblast-like cells. Materials. 2021;14(5):1168. https://doi.org/10.3390/ma14051168
PMid:33801348
19. Mohamed AM. An overview of bone cells and their regulating factors of differentiation. Malays J Med Sci 2008;15:4-12.
PMid:22589609
20. Teitelbaum SL. Osteoclasts: What do they do and how do they do it? Am J Pathol 2007;170(2):427-35. https://doi.org/10.2353/ajpath.2007.060834
PMid:17255310
21. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. J Biol Chem 2010;285:25103-8. https://doi.org/10.1074/jbc.R109.041087
PMid:20501658
22. Chandika P, Jung WK. Marine algae based biomaterials for osteoblast differentiation and tissue regeneration. In: Marine Algae Extracts: Processes, Products, and Applications. United States: Wiley; 2015. p. 489-508.
23. Qu H, Fu H, Han Z, Sun Y. Biomaterials for bone tissue engineering scaffolds: A review. RSC Adv. 2019;9:26252-62. https://doi.org/10.1039/C9RA05214C
24. Cho YS, Jung WK, Kim JA, Choi IW, Kim SK. Beneficial effects of fucoidan on osteoblastic MG-63 cell differentiation. Food Chem. 2009;116:990-4. https://doi.org/10.1016/j.foodchem.2009.03.051
25. Mukhamejanov E, Kurilenko V. Fucoidan: A nutraceutical for metabolic and regulatory systems homeostasis maintenance. World J Adv Res Rev. 2020;6:255-64. https://doi.org/10.30574/wjarr.2020.6.1.0106
26. Zhang R, Zhang X, Tang Y, Mao J. Composition, isolation, purification and biological activities of *Sargassum fusiforme* polysaccharides: A review. Carbohydr Polym. 2020;228:115381. https://doi.org/10.1016/j.carbpol.2019.115381
PMid:31635744