

## Combination of anthocyanin ternatin and hydroxyapatite/ $\beta$ -tricalcium phosphate coralline as a socket preservation biomaterial in dental implant: A narrative review

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### Abstract

**Background:** Tooth extraction is surgical treatment with clinical manifestation is alveolar bone resorption of 11-63% which potentially fails dental implant treatment. Socket preservation is bone regeneration treatment to minimize bone morphological changes in post-extraction using bone graft. Anti-inflammatory biomaterial is needed to modulate inflammatory cascade in the lesion. Anthocyanin ternatin is a flavonoid derived from butterfly pea (*Clitoria ternatea*) as an anti-inflammatory and antioxidants agent. Hydroxyapatite/ $\beta$ -Tricalcium Phosphate coralline (HA/ $\beta$ -TCP coralline) is a combination of bioceramic material from calcium carbonate heating of *Porites* spp. coral which has potential to induce osteogenesis, osteoinduction, and osteoconduction. Combination of Anthocyanin ternatin and HA/ $\beta$ -TCP coralline applied to the defect area in dried powder form to induce hard tissue regeneration.

**Purpose:** To describe the potential of combination of Anthocyanin ternatin and HA/ $\beta$ -TCP coralline as a socket preservation biomaterial in dental implant.

**Review:** Combination of Anthocyanin ternatin and dried powder HA/ $\beta$ -TCP coralline is applied in dental socket. Anthocyanin ternatin suppresses ROS and iNOS then inhibit NF- $\kappa$ B signaling pathway. Downregulation of the pathway decreases TNF- $\alpha$  and IL-1 $\beta$ /6 expression so the expression of RANKL is inhibited. Lowering of ROS followed by upregulated Ca<sup>2+</sup> level from HA/ $\beta$ -TCP coralline causes the increase in DKK1 and PTEN expression so Akt and Wnt expression is induced. Upregulation of the proteins induces the BMP2/TGF- $\beta$ /Smad1/5/8 signaling pathway activation manifest in the increase of Runx2, OCN, and Osx then the preosteoblast differentiation to osteoblast is increased.

**Conclusion:** Combination of Anthocyanin ternatin and HA/ $\beta$ -TCP coralline is potential as socket preservation biomaterial in dental implant.

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**Keywords:** Anthocyanin ternatin; Dental Implant; HA/ $\beta$ -TCP coralline; Medicine; Dentistry.

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## 1. Introduction

Tooth extraction is a surgical treatment with a prevalence of 21.5%. [1] After tooth extraction it can cause clinical manifestations in the form of resorption of alveolar bone around the socket in the vertical dimension of 11-22% and horizontally of 29-63% during the first 6 months. Bone resorption width can reach 3.87 mm whereas bone resorption height reaches 1.67–2.03 mm in the first 3 months after extraction. [2] This condition will reduce the success of stomatognathic function treatments such as dental implants so that treatment is needed to restore bone dimensions. Alveolar. [3]

Socket preservation is a therapeutic procedure to inhibit excessive bone resorption and restore the quantity and quality of bone tissue to near normal after tooth extraction. [4] Considerations for socket preservation are implant delays related to the patient's condition, there are several reasons for delaying dental implants for more than 6 months, and there are plans to use a fixed partial denture in the form of a pontic. [5] Socket preservation can improve implant osseointegration, possess long-term use, and reduce the risk of complications.

Bone graft is a material that acts as a scaffold to increase cell and vascular proliferation and maintain space for new bone regeneration. There are various types of bone graft biomaterials that can be used, namely, autograft, allograft, xenograft, and alloplast. Autograft is biomaterials derived from the same individual, allografts derived from different individuals, xenografts are biomaterials derived from other species, while alloplasts are synthetic materials such as calcium phosphate, polymers, and glass. The use of autograft biomaterials can pose a risk of morbidity for individuals, while allograft biomaterials can transmit disease to patients. The risk of allergies can arise from the use of biomaterials from xenografts and alloplasts. However, the risk of allergies can be reduced through the synthesis of the materials used. [5]

One of the biomaterial innovations as socket preservation for dental implant placement is the combination of Anthocyanin ternatin and hydroxyapatite/ $\beta$ -tricalcium phosphate (HA/ $\beta$ -TCP) coralline. Anthocyanin ternatin is a flavonoid compound from butterfly pea flower (*Clitoria ternatea*) which has potential as an anti-inflammatory agent and antioxidant. [6,7] Hydroxyapatite/ $\beta$ -tricalcium phosphate (HA/ $\beta$ -TCP) coralline is a combination of bioceramic materials from coral *Porites spp.* which are distributed throughout the Indonesian seas and have a trabecular structure similar to bone with a smooth porous surface. HA/ $\beta$ -TCP has high solubility properties which can potentially enhance osteogenesis, osteoconductivity, and osteoinduction. [8-11] The combination of anthocyanin ternatin and HA/ $\beta$ -TCP coralline acts as a scaffold which is applied to the defect area in the form of dried powder to induce regeneration bone, induce colonization of osteogenic cells, and control the inflammatory process in order to repair alveolar bone defect which provide good environment for dental implants insertion. [12] This narrative review is compiled to describe the mechanism of combination of anthocyanin ternatin and hydroxyapatite/ $\beta$ -tricalcium phosphate (HA/ $\beta$ -TCP) coralline as a socket preservation biomaterial in dental implants.

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## 2. Dental Implant

Tooth extraction results in resorption of alveolar bone with clinical manifestations of socket formation. In the first 6 months after extraction, alveolar bone resorption will occur in the vertical dimension of 11-22% and 29-63% horizontally. The decreased volume of bone will form a rounded and flat structure which will reduce the retention and stability of fixed dentures, removable dentures, and dental implants. [2,13] In general, tooth sockets will undergo a process of physiological healing of hard tissue and soft tissue, however, defects in the alveolar bone cannot regenerate completely, so treatment is needed to restore the condition of the alveolar bone. [13] Nowadays, researchers are developing preservation treatments to restore the alveolar bone anatomy. Socket preservation is a procedure in which a graft material is placed in a post-extraction tooth socket with or without a membrane barrier to maintain or increase ridge dimensions for an ideal implant site. [14]

Implants are tooth replacement treatments through surgery on the alveolar bone which consist of prosthetic connection segments, transgingival segments, implant connection segments, and abutments. [15] Insertion of the implant into the alveolar bone will trigger an antigen-antibody reaction which is influenced by the biocompatibility and chemistry of the material. The type of implant that is commonly used today is titanium alloy. Implant placement aims to achieve osseointegration between the alveolar bone and the implant structure. [15]

Dental implant surfaces must have osteogenic properties to optimize osseointegration. In the gingival attachment consisting of soft tissue with cell-adhesive cells, namely keratinocytes and fibroblasts, attention must be paid to the density of the epithelium to prevent bacterial infiltration. Bacterial colonization can cause peri-implantitis. This inflammatory process continues along with bacterial contamination on the implant surface followed by loss of osseointegration due to the host's immunological reaction which causes loss of the implant due to bone loss. Therefore, Trans- as well as supragingival and implant/saliva interfaces must have antiadhesive or antibacterial properties to inhibit biofilm formation. [16]

### 3. Anthocyanin ternatin

*Clitoria ternatea* is a wild plant found in the tropics from the *Fabaceae* family which contains anthocyanin compounds as natural pigments in the form of blue and red pigments in acidic conditions. Ternatin anthocyanins are flavonoids derived from butterfly pea flowers (*Clitoria ternatea*) which have anti-inflammatory, antioxidant and antimicrobial properties.[17] Extraction of anthocyanin ternatin was carried out in several stages. Dried butterfly pea flowers were mashed using a commercial grinder and added to 10 g and then put into a two neck round bottom flask and extracted with 50% ethanol from Sigma Aldrich (USA). Anthocyanin monomers were calculated as cyanidin-3-glycosides using different pHs through various liquid: solid ratios including 10:1; 20:1; 30:1 (mL/g) at 40-80°C for 15-75 minutes. Then, the mixture was centrifuged at 4000 rpm for 15 minutes with a high speed centrifuge Model LACE16 (from COLO lab expert). The supernatant obtained was filtered using filter paper and then put into a bottle to estimate the yield so that a supernatant size of 400-700 nm was obtained. In this extraction process, the highest amount of anthocyanins was at 60.6°C for 46 minutes from a liquid: solid ratio of 23:1 (mL/g) which was about 132,756 mg/L anthocyanins.[19]

### 4. Hydroxyapatite/ $\beta$ -Tricalcium Phosphate Corraline

Coralline hydroxyapatite (CHA) is the result of heating calcium carbonate derived from coral *Porites spp.* with a thickness of 2-5 m and an aragonite core. CHA has high pore interconnectivity and is osteoinductive but cannot induce osteogenesis quickly, so it needs to be combined with  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) to increase osteogenesis and osteoinductivity, as well as promote better biocompatibility and biodegradability.[20]  $\beta$ -TCP is a compound from coral *Porites spp.* which is osteoconductive, high biocompatibility, bioresorbable, non-allergenic, and modulates bone formation. B-TCP has high pore interconnectivity so that it supports the process of bone remodeling by increasing osteogenic cells.[21]

### 5. Discussion

Combination of anthocyanin ternatin and dried powder HA/ $\beta$ -TCP corraline is applied to the tooth socket after extraction. Anthocyanin ternatin inhibits the formation of reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS) so that I $\kappa$ B $\alpha$  phosphorylation by the IKK complex is inhibited which results in inhibition of nuclear factor kappa  $\beta$  (NF- $\kappa$  $\beta$ ) migration to the nucleus. This resulted in a decrease in NF- $\kappa$ B phosphorylation as an inflammatory mediator.[19] A decrease in phosphorylated nuclear factor kappa beta (p-NF- $\kappa$ B) causes inhibition of NLR family pyrin domain containing 3 (NLRP3) activation. NLRP3 is an inflammasome that regulates the expression of pro-inflammatory cytokines. A decrease in NLRP3 resulted in downregulation of tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 1 $\beta$ /6 (IL-1 $\beta$ /6) manifested in a decrease in receptor activator of nuclear factor kappa beta ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) expression.[22-26] A decrease in these two proteins resulted in the lowering of c-Fos and nuclear factor of activated T cells 1 (NFATc1) expression which manifested in a decrease in tartrate-resistant acid phosphatase (TRAP) transcriptional activity. This condition is accompanied by decreased expression of V-ATPase-d2, cathepsin K, and calcitonin receptors which results in inhibition of the process of osteoclastogenesis.[27-30]

The reduction of ROS by anthocyanin ternatin accompanied by the application of HA/ $\beta$ -TCP corraline induced the release of Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> ions causing increased activation of sarcoendoplasmic reticulum calcium ATPase (SERCA), a pump that acts to transport Ca<sup>2+</sup> ion from the cytoplasm into the sarcoendoplasmic reticulum, that is generated by p53. This resulted in an increase in phosphatase and TENSin homolog deleted on chromosome 10 (PTEN) expression so that Wnt expression increased. Wnt then forms a complex with Frizzled protein (FZD) and lipoprotein receptor-related proteins (Lrp5/6) receptors so that dishvelled protein (Dvl) is activated and manifests in the stabilization of  $\beta$ -catenin protein in the cytosol.  $\beta$ -catenin transposes towards the nucleus so that the expression of cyclin D1, Dickkopf-related protein 1 (Dkk1), and Axin2 increases and manifests in proliferation of osteoblast. An increase in these proteins resulted in upregulation of Ras-related protein Rap-1b (Rap1b). This condition, accompanied by an increase in Ca<sup>2+</sup> ions, induces phosphoinositide 3-kinase (PI3K) expression so that protein kinase B (Akt) expression increases. An increase in Akt

causes phosphorylation of Ser2448 in mTOR so that S6K1 in mTOR is activated and manifests in an increase in p70S6K. Increased expression of p70S6K will then induce the activation of bone morphogenetic protein 2/transforming growth factor  $\beta$ /Smad1/5/8 (BMP2/TGF- $\beta$ /Smad1/5/8) signaling pathway manifested in increased expression of Runx2, osteocalcin (OCN), alkaline phosphatase (ALP), and osterix (Ox) thus generating pre-osteoblast differentiation into osteoblasts.[31-43]

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## 6. Conclusion

Anthocyanin ternatin is a flavonoid compound from butterfly pea flower with the ability to inhibit inflammatory pathways by decreasing the expression of ROS and iNOS. HA/ $\beta$ -TCP coralline has high osteoconductivity and osteoinduction properties which play an important role in the bone tissue regeneration. Combination of anthocyanin ternatin and HA/ $\beta$ -TCP coralline applied to the tooth socket after extraction can increase the dimensions of the alveolar bone for preparation of dental implant insertion. According to this review, combination of anthocyanin ternatin and HA/ $\beta$ -TCP coralline may have potential as a socket preservation biomaterial in dental implants.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

There is no conflict of interest in this study.

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