

# THE POTENTIAL OF APATITE CARBONATE AS A SCAFFOLDING MATERIAL FOR TISSUE ENGINEERING IN THE TREATMENT OF ENDODONTIC REGENERATION : LITERATURE REVIEW

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## ARTICLE INFO

### Keywords:

Endodontic regeneration,  
scaffold, carbonate apatite

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## ABSTRACT

Endodontic regeneration treatment is a biological procedure designed to replace the biological structure of damaged teeth. Pulp tissue engineering in endodontic regeneration therapy combines three components, namely stem cells, scaffolds, and growth factors. Apatite carbonate has proven potential as a scaffold for bone regeneration. This study aimed to investigate the potential of apatite carbonate as a scaffold for the regeneration of the pulp dentin complex tissue. The method used is a literature study. Article searches, in English and Indonesian, were conducted through Sciencedirect and PubMed. The articles used are articles published in the last 10 years. The keywords used were endodontic regeneration, scaffolding, and carbonate apatite, then the articles were re-filtered according to the inclusion and exclusion criteria. A total of 12 literatures were included in this review. The results of data synthesis indicate that apatite carbonate is a biomaterial that has biocompatible properties and bioactivity to induce tissue regeneration, especially hard bone tissue. The stability of the material so that it can be modified to adjust its porous size and good biodegradability also supports its potential as a scaffold material. The material also has a chemical structure similar to bone and teeth, so it has the potential to induce the proliferation and differentiation of odontoblasts which are important in endodontic regeneration.

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## 1. INTRODUCTION

The pulp is a soft tissue rich in blood vessels and nerves which has five main functions, namely inductive, formative, nutritive, defensive, and sensitive. When inflammation occurs, the pulp has the ability to perform a defensive reaction, namely by performing a healing. Inflammation of the pulp tissue can occur due to mechanical damage, thermal injury, chemical irritation, and bacteria. Inflamed pulp can cause severe pain, and lead to necrosis, so treatment is needed, namely root canal treatment or what is known as endodontic treatment.<sup>1,2</sup>

Endodontic treatment will eliminate the etiology of pulp damage, retain the tooth in its place, and restore the function of the tooth in the masticatory system. However, endodontic treatment can fail. According to Ingle and Trainor in 1994 root canal filling is a difficult and very critical stage, and the failure rate for endodontic treatment is 58-60%, which is caused by failure at the access preparation stage, biomechanical preparation stage, or poor filling quality.<sup>3</sup> Other failures can also be caused by fracture, as pulp necrosis and massive loss of tooth structure can lead to tooth structure fragility. Therefore, currently being developed an endodontic treatment that aims to restore the vitality of the pulp, for a better success rate of tooth conservation, through Regenerative Endodontic Procedure (REP) or hereinafter referred to as endodontic regeneration therapy.<sup>4,5</sup>

In 1980, Nygaard-Ostby reported on the development of a modern concept of endodontic regeneration, using tissue engineering, through regeneration procedures on young permanent teeth.<sup>6</sup> According to "The American Association of Endodontist (AAE)", endodontic regeneration is a procedure designed based on biological principles, which has the aim of replacing damaged tooth structure, including dentin, root structure, and cells found in pulp tissue.<sup>4,5</sup> The main goal of endodontic

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regeneration is to maintain or restore the vitality of the teeth in cases of infected pulp, both vital and non-vital.<sup>7</sup> The result of endodontic regeneration therapy is healing of vital teeth so that these teeth can return to their proper function.<sup>8,9</sup>

Endodontic regeneration therapy is essentially a vital pulp defense therapy, which involves the use of biomaterials and techniques to induce regeneration of the hard and soft tissues of the teeth. Treatment of pulp capping and apexogenesis is a treatment of pulp vitality defense which is currently widely used. Another endodontic regeneration therapy that has gone through clinical trials and is quite successful is revascularization therapy, in young permanent teeth that have been necrotic. Furthermore, the development of endodontic regeneration led to the engineering of pulp tissue, to restore pulp vitality, in damaged adult teeth.<sup>10</sup>

Important components of pulp tissue engineering in endodontic regeneration therapy are stem cells, growth factors and scaffolds.<sup>6</sup> The first component in tissue engineering techniques is stem cells. Stem cells are cells that have the ability to self-renewal, proliferate, differentiate, and can induce the formation of various types of cells.<sup>11</sup> To facilitate the formation of tissue from stem cells, a framework called a scaffold is needed, which is the second component in tissue engineering.<sup>5</sup> The matrix or scaffold is a three-dimensional structure that is used as a temporary support medium and has properties and structures that support the process of new tissue growth and development.<sup>12</sup> Materials used to form scaffolds are biomaterials that have biocompatibility and biodegradability properties the good one. In addition, for endodontic regeneration, biomaterials with an apatite structure similar to the structure of bones and teeth are also needed, to increase their bioactive properties, thus supporting a faster regeneration process.<sup>5</sup> One of the potential biomaterials in tissue regeneration, especially bone, is carbonate apatite.

Carbonate apatite have been used in medicine, especially in orthopedics, and also in dentistry, as bone grafts and scaffolds for bone regeneration.<sup>13</sup> Carbonate apatite is a biomaterial with a chemical structure of calcium phosphate that can repair or replace bone structure and has biocompatible, bioactivity, and osteoconductive properties for the body.<sup>14</sup> In addition to being biocompatible and bioactive, the material is expected to be accepted in the body, so that it does not cause a response from the body that can have a bad impact, because every foreign object that enters the body will get a response, namely an inflammatory response.<sup>12,13</sup> A study by Aufan et al in 2012 showed that the manufacture of scaffolds with the addition of apatite carbonate was proven to increase the ability of the scaffold to repair damaged tissue. In another study, it was also stated that with the addition of a carbonate component, apatite could affect its properties, such as an increase in solubility, and a relatively lower level of crystallinity like the apatite of human bones.<sup>12</sup>

The structure of bones and teeth have similarities so that these materials support to be used as materials for tissue regeneration, because bones and teeth and these materials have calcium ions which play an important role in tissue regeneration, especially in the endodontic field for pulp capping and endodontic sealers.<sup>15</sup> This is in accordance with research conducted by Zakaria et al in 2017 which showed that with the addition of carbonate apatite, reparative dentin was formed as well as good vitality and no toxicity with the use of these materials.<sup>16</sup>

## **2. METHODS**

### **Research design**

This study used a literature review on several literatures as a reference and analyzed the data obtained by the literature.

### **Research Subject**

Subject of this research is literature taken based on previous research data. Research subjects were adjusted according to inclusion criteria, namely national and international reputable journals in the last 10 years, data was taken regarding apatite carbonate as a scaffold with research results in the form of cell proliferation and differentiation, and exclusion criteria, namely the study did not conduct cell tests, journals were not related to cell regeneration. bones or teeth, and journals in the form of library research,

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not research.

### **Number of Sample**

Number of samples determined by the institution to conduct a literature study is a minimum of 6 main articles. Literature retrieval is done through research keywords. Sampling was adjusted by adjusting the inclusion and exclusion criteria of the study.

### **Aspects of Research Ethics**

There are several things that need to be considered regarding plagiarism, namely:

1. To avoid plagiarism, the author must include the name or agency of the owner of the source.
2. When quoting ideas from these sources, the wording must be reworked from the ideas that have been quoted using their own language without changing the meaning.
3. Do not take over all ideas without an original opinion.

## **3. RESULTS AND DISCUSSION**

This study discusses the potential of apatite carbonate as a scaffold in endodontic regeneration therapy. Scaffolds are biomaterials and function as extracellular matrix. Scaffolds play a role in facilitating stem cells and growth factors to be a place of attachment and a place for the growth of new cells. Apatite carbonate is one of the bioactive biomaterials that is currently in demand. This material has been shown to have several advantages in its properties such as biocompatible, able to stimulate tissue regeneration, and adaptability well. In addition, apatite carbonate is also able to induce remineralization and is a potential biomaterial for various actions in dentistry. literature review will synthesize 12 literatures that have been adapted to the inclusion and exclusion criteria.

The results of research on the literature on scaffolds in tissue engineering show that scaffolds have an important role in providing a microenvironment to help stem cells to adhere to, proliferate and differentiate so as to produce the desired tissue. In the literature Herda and Puspitasari in 2016 concluded that the scaffold for tissue engineering will affect the expected cell growth of the tissue, because the scaffold has a very complex structure and function in terms of size, shape, and type of material. The biomaterial used for tissue engineering in the literature that will be reviewed is currently in the form of bioceramic which is a synthetic scaffold. The literature states that bioceramic scaffolds form the structure of the dentinal pulp by using stem cells in the pulp. These materials have the advantages of small nanostructures, high porosity and high surface area to volume ratio, thereby increasing tissue adhesion.<sup>17</sup>

A similar literature review by Suvarna et al in 2017 demonstrated that the use of scaffolds could create a more practical endodontic tissue engineering therapy, and could be achieved by using a porous polymer scaffold that was highly seeded on stem cells in the pulp. The explanation obtained in the literature is similar to the previous literature that the scaffold must have growth factors to promote cell proliferation and differentiation.<sup>18</sup> Formation of a cell proliferation and differentiation requires three components, one of which is the most important growth factor or growth factor. The growth factor that plays a role in this process in the form of TGF-beta plays a role in providing apoptotic effects. This is very important because it is for cell differentiation and regeneration. properties pleiotropic, and antagonists with cellular effects in adhesion, migration and proliferation, cell differentiation. In in vivo studies, TGF-beta promotes healing and helps to increase granulation tissue, collagen synthesis, connective tissue volume, and angiogenesis. Of these growth factors, besides TGF-beta, VEGF is also the most important mediator in the angiogenesis process and besides that FGF-2 also acts as an early stimulatory factor in the formation of new tissue.

Scaffolds used in tissue engineering must have biocompatible and bioactive properties, because the shape of the porosity, mechanical properties, and pore diameters can be successfully controlled in the preparation technique, one of which is the use of synthetic scaffolds in the form of bioceramics. In the literature Raddall et al in 2019 the use of synthetic scaffolds can avoid the risk of pathogen transmission and have a consistent production process such as mechanical strength.<sup>19</sup> This is in line with the literature review of Yazid et al in 2020 in the treatment of pulp-dentin complex regeneration, scaffolds must have

setting time, namely the use of bioceramics which have better mechanical properties and can improve the biological and physical properties of the scaffold which will improve cell adhesion, proliferation and differentiation.<sup>20</sup> This review was also discussed in the research of Ramadas et al in 2018 and Matsuura et al in 2009 that the use of bioceramics in the form of apatite carbonate provides an ideal environment for cell proliferation and differentiation and the content of this carbonate has the same composition as the mineral structure of bones and teeth which can be initiates the production of odontoblast cells.<sup>21,22</sup>

In endodontic regeneration treatment, the commonly used material is hydroxyapatite or MTA which is a class of bioceramic materials and its mineral structure is carbonate apatite, because its mineral structure can improve the surface characteristics of the scaffold, its roughness, as well as stem cell viability and proliferation.<sup>23,24</sup> In the literature of Nomura et al in 2016 apatite carbonate can be used as a scaffold because it has a porous structure, so it can be a medium for transporting nutrients and oxygen.<sup>25</sup> The material can also be gradually degraded due to its bioresorbable which will turn into the surrounding tissue structure. Degraded scaffolds should not be toxic and should be easily cleaned or absorbed to minimize the risk of an inflammatory response.<sup>19,26</sup> Apatite carbonate has been carried out on bone with the results of SEM examination by research conducted by Kamadjaja et al in 2016 and Saskianti et al in 2017 showing that the use of a scaffold with apatite carbonate material has a three-dimensional structure with many pores that can stick together and proliferate. between the porosities of the scaffold. But carbonate apatite has a cylindrical outer surface and the absorption of nutrients from the cell is not much, when compared to hydroxyapatite.<sup>27,28</sup>

Apatite carbonate has been shown to stimulate tissue with the formation of new tissue, because its calcium ion plays an important role in the differentiation of pulp cells.<sup>29</sup> Research conducted by Zakaria et al in 2017 examining the teeth of wistar rats showed that there was reparative dentin formed after the third week of application using apatite carbonate. Reparative dentin is formed from the remaining odontoblast cells or undifferentiated mesenchymal cells. In primary and secondary dentin, odontoblast cells are regularly located in the outer layer of the pulp and are the key to dentin formation (dentinogenesis). If the cells are damaged, their function will be replaced by stem cells (DPSCs) or undifferentiated mesenchymal cells from the pulp core as precursor cells, and differentiate into odontoblast-like cells or osteodentin. The morphology of odontoblast-like cells in this study appeared on the fourteenth day and the dentin bridge formed on the fourth week. The teeth that were applied with apatite carbonate showed good vitality and function at the time of histological examination, and there was no further infection in the periapical area, so the procedure was declared successful.<sup>16</sup>

On the results of previous studies in line with the research of Sabirin and Zakaria in 2020, it was proven that apatite carbonate can form reparative dentin after 21 days of application.<sup>30</sup> Reparative dentin is a tertiary dentin matrix released by odontoblast-like cells in response to a stimulus following the death of postmitotic odontoblasts responsible for the secretion of secondary dentin. Then reparative dentinogenesis involves a rarer sequence of biologic events than reactionary dentinogenesis, because it involves the presence of progenitor cells or growth factors and the induction of differentiation of odontoblast-like cells.<sup>31</sup> In the studies that have been carried out, histologically there were no signs of inflammatory conditions in these samples. In addition to testing on mice to see the formation of reparative dentin, a study conducted by Tjahawati et al in 2020 conducted a study of endodontic sealers using apatite carbonate material. The results obtained using the subcutis back of wistar rats showed that there was no toxicity seen by histological examination.<sup>32</sup> This is similar to the study of Zakaria et al in 2020, apatite carbonate has good mechanical properties and can release calcium ions and has an alkaline pH that can contribute to antimicrobial activity and histologically there is no toxicity to the material and can maintain pulp vitality.<sup>29</sup>

The formation of tissue regeneration in the pulp is formed from odontoblast cells, one of which is from the study of Zakaria et al in 2020, the formation of reparative dentition which is influenced by the presence of remaining odontoblasts or undifferentiated mesenchymal cells. This was explained in the research of Ishikawa and Hayashi in 2021 and Ferreira et al in 2021 which showed that apatite carbonate

has absorption or bioresorbable capacity and has an influence on the formation of a cell proliferation and differentiation. The formation of tissue regeneration in the pulp is formed from odontoblast cells, one of which is from the study of Zakaria et al in 2020, the formation of reparative dentition which is influenced by the presence of remaining odontoblasts or undifferentiated mesenchymal cells. This was explained in the research of Ishikawa and Hayashi in 2021 and Ferreira et al in 2021 which showed that apatite carbonate has absorption or bioresorbable capacity and has an influence on the formation of a cell proliferation and differentiation.<sup>33,34</sup> Based on this study, it is the same as that of Hayashi et al. in 2022 with the use of an apatite carbonate scaffold to increase the rate of resorption, resistance to compression of soft tissue, and the height and volume of tissue increased.<sup>35</sup> Apatite carbonate is a bioceramic material that has been reviewed in several literatures having the same properties and structure as teeth.<sup>36</sup> Apatite carbonate can be used as a scaffold because it has the properties and structure, has good adaptability and adhesion, so that it can be a medium for nutrient and oxygen transport.<sup>25</sup> This is evidenced by the study of Zakaria et al in 2020, the material has good adaptation and adhesion without leaving gaps. Apatite carbonate can also release calcium ions and has an alkaline pH that contributes to antimicrobial activity, lacks toxicity, and can maintain pulp vitality.<sup>29</sup>

#### 4. CONCLUSION

From the results literature review, it can be concluded that apatite carbonate has good potential to be used as a scaffold material in endodontic regeneration treatment. Apatite carbonate has biodegradable, biocompatible properties, good porosity and stability, as well as calcium phosphate content which can support the regeneration of the dentin-pulp complex tissue.

#### CONFLICT OF INTEREST

We declare that there is no conflict of interest in the scientific articles we write

#### ACKNOWLEDGEMENT

Our thanks go to the professionals who have helped research and the preparation of papers, namely lectures and examiners of the Faculty of Dentistry, General Achmad Yani University

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