THE ROLE OF HYDROXYAPATITE EXTRACT AS A BIOACTIVE INGREDIENT IN DENTISTRY

A LITERATURE REVIEW

THESIS

Submitted as Partial Fulfillment of Requirements

Achievement of a Bachelor's Degree in Dentistry

ANDI ZHIRAH SAPADA

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DEPARTMENT OF DENTAL MATERIAL

FACULTY OF DENTISTRY

HASANUDDIN UNIVERSITY

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Hereby declare that the thesis titled "The Role of Hydroxyapatite Extract as A Bioactive Ingredient in Dentistry" is my own original work, and no plagiarism has been done in its writing. Any citations in this thesis have been given due acknowledgements and have their sources quoted and listed. I am willing to carry out the proper process in accordance with the applicable laws and regulations if it turns out that this thesis is partly or entirely plagiarized from other works.

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PREFACE

بِسْمِ اللهِ الرَّحْمٰنِ الرَّحِيْمِ

All praise and gratitude to Allah SWT for all His blessings and guidance so that the author can complete the writing and preparation of the thesis titled **"The Role of Hydroxyapatite Extract as A Bioactive Ingredient in Dentistry"** This thesis was written as a requirement for the completion of studies in achieving a bachelor's degree in dentistry at the Faculty of Dentistry, Hasanuddin University. Salawat and greetings are also extended to the great Prophet Muhammad SAW as an example who leads people from a dark path to a path of knowledge.

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The author is fully aware that this thesis is still far from perfection, because perfection belongs to Allah alone. Therefore, the author apologizes if there are errors in writing this thesis. We appreciate criticism and suggestions for the improvement of similar writing in the future. The author hopes that this thesis can be useful and can be of positive value for all parties who need it.

Makassar, 09 August 2022

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ABSTRAK

The Role of Hydroxyapatite Extract as A Bioactive Ingredient in Dentistry

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Latar Belakang: Hidroksiapatit (Ca10(PO4)6(OH)2) merupakan mineral anorganik yang terbuat dari bahan kimia sintetik atau biomaterial alami seperti cangkang telur, sisik ikan, gipsum, dan tulang. Kalsium yang terkandung dalam tulang adalah 7,07% CaCO3, 1,96% CaF2, dan 58,30% Ca3(po4)2. Hidroksiapatit bersifat biokompatibel dan ditoleransi dengan baik oleh jaringan pada rongga mulut manusia. Hidroksiapatit memiliki sifat osteokonduktif, merangsang perkembangan osteoblas dan produksi tulang. Penggunaan hidroksiapatit dalam kedokteran gigi untuk rekonstruksi jaringan tulang, rekayasa jaringan lunak, pelapisan implan gigi, perawatan efek periodontal dan bahan restoratif seperti resin komposit dan GIC. **Tujuan:** Mengetahui aplikasi ekstrak hidroksiapatit sebagai bahan bioaktif dalam kedokteran gigi. **Metode:** Perancangan penulisan ini adalah literature review. **Kesimpulan:** Saat ini penggunaan ekstrak hidroksiapatit telah banyak digunakan di bidang kedokteran gigi karena memiliki banyak keunggulan, salah satunya adalah sifat bioaktif dan biokompatibilitasnya.

Kata kunci: Ekstrak Hidroksiapatit, Hidroksiapatit dalam Kedokteran Gigi, Bahan Bioaktif

ABSTRACT

The Role of Hydroxyapatite Extract as A Bioactive Ingredient in Dentistry

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Background: Hydroxyapatite (Ca10(PO4)6(OH)2) is an inorganic mineral this material can be made from synthetic chemicals or natural biomaterials such as egg shells, fish scales, gypsum, and bone. Calcium contained in bone is 7.07% CaCO3, 1.96% CaF2, and 58.30% Ca3(po4)2. Hydroxyapatite is highly biocompatible and well tolerated by human oral tissues. Hydroxyapatite has osteoconductive properties, stimulating osteoblast development and bone production. The advantages of this biomaterial can be used in dentistry such as bone tissue reconstruction, soft tissue engineering, dental implant coatings, treatment of periodontal effects, and restorative materials such as composite resins and GIC. **Purpose:** Knowing about the application of hydroxyapatite extract as a bioactive ingredient in dentistry. **Method:** The design of this paper is a literature review. **Conclusion:** Currently the use of hydroxyapatite extract has been widely used in all fields of dentistry because hydroxyapatite has many advantages, one of which is its bioactive properties and biocompatibility.

Keywords: *Hydroxyapatite extract, Hydroxyapatite in dentistry, Bioactive ingredient*

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CHAPTER 1

INTRODUCTION

1.1. Background

Hydroxyapatite (Ca10(PO4)6(OH)2) is an inorganic mineral that can be made from synthetic chemicals or natural biomaterials such as egg shells, fish scales, gypsum, and bone. Bones contain elements such as calcium and phosphorus. Calcium contained in bone is 7.07% CaCO3, 1.96% CaF2, and 58.30% Ca3(PO4)2 and phosphorus content in bone is 2.09Mg3(PO4)2 and 58.30% Ca3(PO4). Calcium and phosphorus are the main constituents of hydroxyapatite, so the bone can be used as raw materials for the synthesis of hydroxyapatite. Regarding its chemical content, animal bones can be used as an adsorbent in the adsorption process.[1.2]

Hydroxyapatite is the terminal hydroxyl member of the apatite group complex. The OH- ion can be replaced by fluoride, chloride, or carbonate to give fluoroapatite or chlorapatite. These compounds form crystals in the hexagonal crystal system. Pure hydroxyapatite powder is white in color. However, natural apatite can be brown, yellow, or green. Hydroxyapatite crystals are also found in small spots of calcification, such as in the pineal gland and other structures are known as the *corpora arenacea* or "brain sand". Human bone is a modified form of hydroxyapatite known as a mineral substance. Hydroxyapatite, which

lacks carbonated calcium, is the main mineral constituent of enamel and dentin in teeth.

The method of synthesizing hydroxyapatite from animal bones can be carried out in various ways, such as the Sol-Gel method, the wet precipitation method, acid hydrolysis, and also wet hydrolysis. Bones are one part of animals that have many benefits and can be used for various purposes. Animal bones that can produce hydroxyapatite include beef bones, fish bones, and chicken bones.

Hydroxyapatite is highly biocompatible and well tolerated by human oral tissues and has osteoconductive properties, stimulating osteoblast development and bone production. The advantages of this biomaterial can be used in dentistry such as bone tissue reconstruction, soft tissue engineering, treatment of periodontal defects, dental implant coatings, as restorative materials such as composite resins and GIC.

Bioactive compounds are essential and non-essential compounds that we can find in nature. These compounds are also part of the food chain that affects human health.[4] Bioactive compounds also known as *nutraceuticals* act as natural elements of food and provide health benefits to the nutritional value of foods. Bioactive compounds found in the bodies of animals and plants have several benefits for human life, including as a source of antioxidants, antibacterial, anti-inflammatory, and anticancer.[5]

Based on the explanation that has been written above, the purpose of choosing *a literature review* is to find out more about the role of hydroxyapatite extract as a bioactive ingredient in dentistry.

1.2. Formulation of the problem

Based on the background described above, the formulation of the problem in this *literature review* is: What are the role of hydroxyapatite extract as a bioactive ingredient in dentistry?

1.3. Writing purpose

Based on the formulation of the problem above, the objectives of this paper are:

A. General writing purpose

Knowing about the role of hydroxyapatite extract as a bioactive ingredient in dentistry.

B. Specific writing purpose

Knowing the role of hydroxyapatite extract as a bioactive ingredient in several dental treatments such as prosthodontics, conservation, oral and maxillofacial surgery, and periodontics.

1.4. The benefits of writing

Some of the benefits of this writing are:

A. Theoretical benefits

As information material and can increase knowledge about hydroxyapatite extract as a bioactive ingredient in dentistry.

B . Practical Benefits

The results of this *literature review* are expected to be used to conduct further research on the benefits of hydroxyapatite extract as a bioactive ingredient in dentistry.

CHAPTER 2

LITERATURE REVIEW

2.1. Hydroxyapatite

Hydroxyapatite is one of the bioceramics that has recently been intensively researched, especially related to its application in the medical world. In general, hydroxyapatite is widely used for bone regeneration, bone and dental implants, and orthopedics. The extent of its application is inseparable from the important properties of hydroxyapatite, namely osteoconductive, biocompatible, and non-toxic.[6]

Biocompatible, bioactive, and bioabsorbable are important chemical properties that we can find in hydroxyapatite extract. Biocompatible means that the material does not trigger a reaction against the human immune system. Bioactive substances are substances that can cause a biological reaction between the implant and the tissue. The bioabsorbable material dissolves over time regardless of the mechanism leading to material transfer andallowings newly formed tissue to grow on any surface.[7]

The advantage of using hydroxyapatite as a bioceramic or biomaterial is its similarity to the inorganic components of bones and teeth. Hydroxyapatite which is highly biocompatible and does not cause an inflammatory response can be used as a biomaterial in medicine and dentistry.[8] Hydroxyapatite is included in the category of bioactive ingredients

that are rich in Ca and PO4 substances so that they can obtain specific biological responses between tissues and materials. The hydroxyapatite products can be categorized in the form of blocks and granules obtained by chemical sintering with a porosity of 100-300 m.[9]

The composition of hydroxyapatite is very diverse, the word 'apatite' defines a family of compounds with similar structures: hexagonal system, space group, P63/m. In addition, hydroxyapatite is chemically unstable thermally because it decomposes at a temperature of 800 to 1200 degrees Celsius, depending on stoichiometry.[10]

Hydroxyapatite has hexagonal symmetry and unit cell lattice parameters = 0.94 nm and c = 0.68 nm. Taking into account the lattice and symmetry parameters, the unit cells are considered to be arranged along the c-axis. This orientation can give rise to growth along the c-axis and a needle-like morphology.[11] Hydroxyapatite consists of component atoms that are configured and can take the form of a crystalline or amorphous phase. Determination of structure and phase can be determined by the diffraction of absorbance peaks.[12]

Hydroxyapatite is most similar to the mineral part of the bone. The chemical formula Ca10(PO4)6OH hydroxyapatite is the most thermodynamically stable crystalline phase of Ca/P. The crystal structure of hydroxyapatite can be monoclinic or hexagonal. The monoclinic hydroxyapatite structure was obtained only in pure condition with a

stoichiometric composition, with a Ca/P ratio of 1.67. The hexagonal structure is generally obtained from the non-stoichiometric synthesis of hydroxyapatite. The lower the value of the Ca/P molar ratio, the more acidic and the more soluble the calcium orthophosphate compound.[13]

Characteristics of the general crystal structure of the hexagonal system, the cell dimensions are a = 9.423 and c = 6.875. This material can be obtained from the body itself (autograft), from other humans (allograft), and animals (xenograft). The use of autografts does not cause a rejection reaction from the body, only its availability is limited and requires surgery. Allografts and xenografts sometimes cause bodily rejection reactions, can be a means of disease transmission, an are of limited availability.[14]

2.2. Synthetic Hydroxyapatite

Hydroxyapatite can be found in natural materials that have high calcium levels so that they can produce good hydroxyapatite. Hydroxyapatite can be produced from inorganic or organic sources. Inorganic sources such as rock containing phosphate and organic sources come from chicken egg shells, shells, fish bones, and beef bones.

Hydroxyapatite used for industrial applications is generally obtained by synthetic methods. Synthetic methods that are often used to produce hydroxyapatite are hydrothermal, sol-gel, ultrasonic irradiation, microwave irradiation, and precipitation methods.

The hydrothermal method is the most appropriate method to get results with good quality, purity, reactivity, and yield.[15] This method is also relatively simple and inexpensive in the process. In addition, previous studies reported that the hydroxyapatite produced by the hydrothermal method was the most homogeneous. To improve the performance of hydroxyapatite in various fields of application, it is usually enhanced by forming a composite.[16]

The sol-gel method can be used to produce fine hydroxyapatite crystals. Porous hydroxyapatite is made from calcium obtained from the material to be used with the addition of phosphoric acid and chitosan. The sol-gel process begins with the formation of colloids that have suspended solids in solution, this condition is called sol. This sol will then undergo a phase change into a gel, which is a colloid that has a larger solid fraction than the sol. This gel will undergo a solid phase change to become hard, and then be heated to form a ceramic.[17]

The ultrasonic method is the easiest process to produce hydroxyapatite which is efficient for refining, dispersing, and preventing agglomeration of particles and is economical and easy to operate without the need for expensive equipment in a scale-up process with uniform size and morphology.[18]

The microwave irradiation method or commonly called the microwave method is an alternative to increase efficiency in organic reactions. In addition to having the advantage of accelerating chemical reactions, the use of microwave irradiation can also cause damage to the chemical structure of the

product and the occurrence of other side reactions. This hydroxyapatite synthesis has several advantages, namely shorter synthesis time, regular heating, fast reaction, easy to produce, sloping particle distribution which has a high yield, high purity, and efficient energy transformation through uniform heating.[19]

The precipitation method is a method of deposition of each base material with a reactant. The precipitation results are then combined to form the desired compound stoichiometrically. The precipitation method is carried out by dissolving the active substance in a solvent, then adding another non-solvent solution. This causes the solution to become saturated and rapid nucleation occurs to form nanoparticles.[20]

Hydroxyapatite can be found in natural materials that have high calcium levels so that they can produce good hydroxyapatite. Hydroxyapatite can be produced from inorganic or organic sources. Inorganic sources such as rock containing phosphate, while organic sources come from chicken egg shells, shells, fish bones, and beef bones.[21]

2.2.1. Egg Shell

Chicken egg shells can be used for hydroxyapatite synthesis because they contain 94% $CaCO_3$. The high levels of calcium in chicken egg shells provide a good potential opportunity to replace synthetic calcium and calcium

from beef bones which are generally more expensive economically and more difficult to prepare.[22]

The chicken eggshell consists of organic and inorganic phases. The inorganic phase consists of 69% hydroxyapatite crystals, 22% organic phase mainly consists of type I collagen, and 9% water. The deposition method is the most widely used because it is simple, inexpensive, and easy.[23.24] Pure hydroxyapatite powder contained in chicken egg shells can be used to improve the mechanical properties of dental restorative materials, one of which is glass ionomer cement (GIC).

Glass ionomer cement is a self-adhesive restorative material. Glass ionomer cement is a water-based cement formed by an acid-base reaction between glass fluoroaluminosilicate powder and a carboxylic acid copolymer solution. Glass ionomer cement has a tooth-like thermal coefficient, chemically bonds to enamel and dentin, and is biocompatible. However, glass ionomer cement is brittle and has low wear resistance, so the use of glass ionomer cement as a restorative material is limited to cavities that do not receive great stress.

The addition of hydroxyapatite to glass ionomer cement powder can increase the compressive strength, tensile strength, and flexural strength of glass ionomer cement. The addition of nano-sized hydroxyapatite-silica with various concentrations made by sol-gel technique on glass ionomer cement powder. When the glass ionomer cement powder containing hydroxyapatite

mixes with the liquid glass ionomer cement, the calcium ions in the hydroxyapatite will be involved in the acid-base reaction with the liquid so that after the gelling phase, more salt bridges are formed and a cross-linking structure is formed. Surface hardness is very important for dental restorative materials, including GIC, because it affects the ease of finishing and polishing of the material as well as the resistance of the material to scratches.[25.26]

2.2.2. Clam Shells

Hydroxyapatite can also be found in clam shells. This material is very easy to find in Indonesia. However, it has not been put to good use. The manufacture of hydroxyapatite powder from shellfish is very helpful in processing shellfish waste which has been causing environmental problems.[7]

The benefits of using clam shells are that they can increase the selling value of shellfish, reduce solid waste in the environment, and use natural materials as a substitute for bone components. Therefore, this idea is a solution that has the potential to be developed. The different techniques that have been developed and used in the synthesis of hydroxyapatite will produce hydroxyapatite particles with different characteristics.[27]

Hydroxyapatite powder obtained from shells can be useful in the field of dentistry, namely as a mixture of synthetic denture materials and also for bone graft material. The mixture of hydroxyapatite powder from shells with acrylic powder in imported dental materials produces mechanical properties

and can be used as a new substitute material, thereby reducing dependence on imported materials.

Acrylic resins are polymer chains consisting of repeating methyl methacrylate units. Acrylic resins are used to make denture bases in the rehabilitation process, for orthodontic plates, as well as crown and bridge restorations. Hot polymerized acrylic resin is a denture base material that is often use, because the acrylic resin has aesthetic advantages and a relatively cheap price, but hot polymerized acrylic resin must have good strength to be able to withstand masticatory loads in the mouth.

Hydroxyapatite from blood clam shells (Anadara granosa) is a bioceramic material containing calcium and phosphate, and can be used as a filling material to increase the strength of denture plates. Porous hydroxyapatite applied as a denture pore will affect the strong press of the denture. The more pores there are, the lower the compressive strength.

An important factor in designing a dental prosthesis is the strength or mechanical properties of the material which ensures that the denture functions effectively, safely, and lasts for a certainperiode. In general, strength refers to the ability of a prosthesis to withstand applied forces without breaking or deforming excessively. Mechanical properties are measurable responses both elastic (reversible or can return to its original shape when the pressure is released) and plastic (irreversible or unable to return to its original shape or not elastic), of a material when exposed to a force or pressure distribution.

A category of physical properties is a group of mechanical properties that appear most often expressed in units of pressure and stress. Compared to alloys such as Co/Cr and stainless steel, acrylic resin is a soft, weak and flexible material. Denture bases are made of adequate thickness, rigid and strong. Acrylic resins also have a relatively low impact on strength and if these bases are dropped on a rough surface, the probability of fracture is high. Impact strength is essentially a measure of the toughness of a material as it measures the energy required to initiate cracking through a specimen of known dimensions. Crazing can sometimes occur on the surface of the acrylic resin. This is a series of surface cracks which have the effect of weakening the base.[7]

2.2.3. Fish Bone

Fish bones can be used as a natural base material to make hydroxyapatite. The main components of fish bones are calcium, phosphate, and carbonate, while magnesium, sodium, strontium, tat, chloride, hydroxide, iron, sulfate, and selenium are present in small amounts. [28.29] The waste candidate used in the synthesis of hydroxyapatite must have a high calcium content because hydroxyapatite is extracted through the reaction between calcium precursor and phosphate precursor.[30.31]

Fishbone waste such as mackerel, cork, and tuna is one of several types of fishbone waste that can be used as a calcium precursor in the

synthesis of hydroxyapatite because it is rich in calcium, phosphorus, and carbonate. Hydroxyapatite obtained from fish bone base material can be used in the manufacture of composite resins that can be used as dental restorative materials and also for bone filler.

Hydroxyapatite has been studied for many years and is widely used for the manufacture of implants due to its similarity to the bone mineral phase and proven biocompatible with human bones and teeth. Hydroxyapatite is able to undergo osteogenesis binding and is relatively insoluble in vivo. Many studies have shown that hydroxyapatite does not show toxicity, inflammatory response, pyrogenetic response (causing fever).

In addition, the formation of fibrous tissue between the implant and bone is very good, and has the ability to directly bond with the host bone. Hydroxyapatite exhibits bioactive and osteoconductive properties which are very beneficial in the process of bone mineralization. Composites are expected to have good mechanical properties for application purposes bone filler. In addition, it is hoped that the addition of chitosan can increase the osteoconductivity of hydroxyapatite, so that it can accelerate the formation of bone minerals.[32]

2.2.4. Beef Bone

Beef bones have a fairly high calcium content, which is around 85.84%. Due to the high calcium content, calcium can be used for the synthesis of hydroxyapatite. Beef bone is used as a source of calcium and phosphoric acid (H3PO4) as a source of phosphate.[33]

Beef bones contain a mineral composition in the form of elements of calcium and phosphorus. Calcium contained in beef bones is 7.07 in the form of CaCO3, 1.96 in the form of CaF2, even 2.09 in the form of Mg3 (PO4)2, and 58.30 in the form of Ca3 compounds. (PO4) 2. The content of calcium and phosphorus can be used as the main raw materials in the synthesis of hydroxyapatite bioceramics.[34]

Synthesis of hydroxyapatite from bovine bone was carried out by dry method and sol-gel method. In addition to these two methods, another method that can be used to synthesize hydroxyapatite from bovine bone is the wet method. The use of this wet method has the advantage that it has a relatively low cost, and produces hydroxyapatite with a fairly high level of purity.[33.35]

Beef bones have almost the same composition as human bones because every mammal bone has the same mineral, organic, and water composition. Beef bone can be used as a source of hydroxyapatite and collagen to be used as implants and bone graft in human bones.

Bone graft is a material that serves to assist reconstruction, stabilize the structure and bond in the bone and stimulate the process of osteogenesis

and healing of large bone defects. Hydroxyapatite has the ability of osteoconduction and osteoinduction so that it can stimulate osteogenesis. The definition of osteoconduction, is that in its function as a scaffold, bone graft is able to become a medium for stem cells and osteoblasts to attach, live and develop properly in bone defects.

Scaffold also helps the formation of blood vessels in the formation of new bone. Osteoconductive grafts can stimulate bone growth and cause bone apposition of existing bone. The osteoconductive properties of a material are influenced by its shape and structure, including the degree of porosity, pore size, the relationship between pores, and surface roughness.

Hydroxyapatite is osteoconductive, which is able to induce and stimulate stem cells and osteoblasts to proliferate and differentiate in the formation of new bone or the process of bone regeneration. The osteoinduction process functions to stimulate osteogenesis, meaning that the bone graft actively stimulates and induces stem cells and osteoblasts from the surrounding tissue to proliferate and differentiate in the formation of new bone.

Several growth factors play a role in the differentiation and proliferation of osteoblasts, including bone morphogenic proteins (BMPs), platelet-derived growth factors, insulin-like growth factors (I and II), fibroblast growth factors (acidic and basic,) epidermal growth factor, TGF. -β (β1 and 2) and retinoic acid.

The process of new bone formation begins with the inflammatory phase, in this phase the formation of blood clots occurs. The inflammatory phase occurs between the first week to the second week. At the cellular level, inflammatory cells (neutrophils, macrophages and phagocytes) and fibroblasts will infiltrate the wound area stimulated by prostaglandins. Inflammatory cells together with osteoclasts function to clean necrotic tissue, as well as to prepare for the repair phase. Infiltration of these cells gives rise to granulation tissue, increases vascular growth and migration of mesenchymal cells so that the fractured area gets a good supply of oxygen and nutrients.

Then the repair phase occurs, the bone graft will stimulate growth by inducing and becoming a medium for stem cells and osteoblasts to attach, live and develop properly in the bone defect. hydroxyapatite was able to create a suitable atmosphere as well as become a medium for the attachment of stem cells in bone defects so that they can differentiate into mature osteoblasts so that the process of osteogenesis can be produced by hydroxyapatite as a scaffold in the process of bone regeneration.[36]