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Polymeric Scaffolds for Dental Pulp Regeneration with Tissue Engineering Approach

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ABSTRACT: The challenge in dentistry nowadays is to revitalize the dental pulp by utilizing tissue engineering technology, thus a biomaterial is needed to facilitate the process. One of the three essential elements in tissue engineering technology is scaffold. Scaffold acts as a three-dimensional (3D) framework that will provide structural and biological support, and create a good environment for cell activation, communication between cells, and induce cell organization. Therefore, selection of scaffold is a challenge in regenerative endodontics. Scaffold must be safe, biodegradable, biocompatible, low immunogenic, and able to support cell growth. Moreover, it must be supported by the adequate characteristics of scaffold which include the level of porosity, size, pores, and interconnectivity which will ultimately play an essential role in cell behavior and tissue formation. The use of natural or synthetic polymer scaffolds as a matrix in dental tissue engineering, with excellent mechanical properties such as small pore size, high surface-to-volume ratio, has recently received a lot of attention because it shows great potential with good biological characteristics for cell regeneration. This review will describe the latest developments regarding the usage of natural or synthetic scaffold polymers with ideal biomaterial properties to facilitate tissue regeneration combined with stem cells and growth factors in revitalizing dental pulp tissue.

Keywords: biocompatible; biodegradable; polymers; scaffolds; tissue engineering.

INTRODUCTION

Pulpal pathosis is one of the most common oral diseases because of persistent stimulation from trauma, dental caries, or iatrogenic cause. Dental caries is occurred because of bacterial infection on tooth surface, which consist of enamel and dentin. Untreated dental caries would trigger inflammation response in dental pulp, and chronic inflammation in pulp tissue would lead to permanent healthy tissue loss.[1,2]

Current pulpal pathosis treatments are root canal treatment and pulp revascularization.[2] Root canal treatment is the treatment choice in dentistry which effective for of severe pulpal pathosis conditions. This treatment has high success rate, but the tooth would loss pulp tissue afterwards. Thus, despite the treatment benefit, the treated tooth would become non vital which increase the risk of fracture, decrease in pulp defense mechanism and sensory function.[2,3]

Therefore, regenerative endodontic treatment to restore normal pulp function through complex dentin-pulp regeneration, is recently being developed. The treatment aimed for replacing the pathological or non-vital pulp tissue with new healthy tissue.[2,4]

Tissue regenerative engineering technology is improving rapidly nowadays. In pulp tissue regeneration, three important aspects were developed to be utilized: stem cell, growth factor, and biomaterial/scaffold.[2,5] Stem cell is one of the key elements in tissue engineering technology. Stem cell is unspecialized cell which had ability to regenerate, proliferate, and differentiate into specific cells.[6,7] These cells would play role in healing after injury through tissue regeneration.[2,8]

Growth factor or morphogen is a protein or signaling molecule which bonds with specific membrane cell's receptor which would controls and coordinates all cellular function, such as cell signaling, cell proliferation, and matrix synthesis.[6,9] Growth factor has important role in increase the stem cell's regenerative effect and control function. Example of growth factors which play a role in signaling process of dentin and pulp regeneration are Bone Morphogenic Protein (BMP), such as BMP-2, BMP-4, BMP-7, and Transforming Growth Factor β-1(TGF-β1).[4,10,11]

Scaffold or biomaterial is a framework or structure which works in providing three-dimension (3D) growth space for cells and regulates the cell's function and metabolism. Scaffold would create a micro environment which benefits to accomplish cell's regenerative capacities and multipotentialities. The conditions will promote the tissue regeneration. Recently, many natural or synthetic scaffold materials used for pulp regeneration.[2,12] Bioactive scaffold would stimulate stem cell's proliferation and differentiation into odontoblast like cells to regenerate pulp tissue.[13,14] Therefore, role of scaffold in tissue regeneration were important, which is become the mediator which facilitate the transfer of stem cells and/or growth factors at the local receptor.[15]

Each component in tissue engineering has a different effect in supporting the pulp regenerative process, but a combination of these three components will give the best results.[2,4] Dental tissue engineering is expected to provide vital tooth with pulp tissue similar with normal tooth. Therefore, it is important to guide the cell interaction with extracellular matrix which could be obtained by scaffold and cell culture technique.[15]

THE DENTAL PULP

Dental pulp is a loose connective tissue which occupied the root canal and surrounded by dentin. Dental pulp consists of blood vessels, nerves, and odontoblasts which lined the pre-dentine in pulp tissue. Thus, pulp has roles to provide nutrition, vitality, and pathogen detection through its sensory function for infection responds. Pulp tissue has sensitivity and immunoprotective attributes which could maintain pulp homeostasis, has regenerative ability, and form reactionary dentin.[2,16–18]

Histologically, dental pulp consists of several zones, which are dentinoblastic zone, cell-free zone, cell-rich zone, and pulp core. Primary cells of the pulp are odontoblast, fibroblast, macrophage, undifferentiated ecto-mesenchymal cell, and other immunocompetent cells.[19,20]

Dentinoblastic zone functionally would forms pulp-dentin complex. This zone is the first line of reparative dentine formation and will provide protective responds towards external stimulation. While pulp core is rich of nerves and blood vessels, which will provide nutrition and sensory function to the pulp.[2,19]

Therefore, loss of pulp tissue would cause loss of vitality and sensitivity of the tooth, and lead to uncontrolled infection to surrounding tissues. This condition needs complex treatment, such as root canal treatment, which make the tooth become non vital and brittle, then influence patient's quality of life.[17,18]

DENTAL PULP REGENERATION

Pulp regeneration is a healing process of injured or loss part of dental pulp, which resulted re-establishment of its complete biological function.[2,21] Ideal pulp regeneration should generate pulp structure and function as similar as possible with healthy tissue. This regeneration involved dentin-pulp complex regeneration, blood vessels, and nerves regeneration which reached favorable reconstruction through angiogenesis and neurogenesis process. Other than that, it also involved rehabilitation of pulp physiological function, such as sensation, nutrition, and immunological defense.[2,6]

Successful pulp regeneration illustrated by formation of connective tissue with cell density and architecture similar with healthy pulp, consist of nerves and blood vessel, and able to secret new dentin formation with controlled rate as healthy pulp. The vascular tissue will play a role on providing nutrition, oxygen, immune cell, and recruitment of circulation cell, which will maintain the tissue's vitality and viability. While the nerves are fundamental to cell regulation which manage the regeneration process, provide defense mechanism, and tissue repair.[6,22]

Regenerated blood vessels should be connected with bone periapical tissue in tooth which surround the tooth, therefore it can receive blood flow regularly from the circulation and transport the nutrition for regenerating tissue or dentin. Other than that, regenerating tissue should be innervated, thus the tooth could maintain the heat/cold and pain sensation.[17,23] Therefore, vascular and nerves supply should be maintained through the apical foramen which is one the aim of pulp regenerative process.

In the regeneration process, stem cell will be proliferated and differentiated into endothelial cell for angiogenesis/vasculogenesis and into odontoblast for forming of dentin reparative

process. At the beginning angiogenic signal like fibroblast growth factor (bFGF), vascular-endothelial growth factor (VEGF), and transforming growth factor β (TGF-β) will be released by endothelial cell, injured pulp cell, and extracellular matrix (ECM) which caused the stem cell migration and stimulates the neo-angiogenesis.[24,25]

ROOT CANAL TREATMENT (RCT)

Infected dental pulp needs the root canal treatment (RCT), which is conservative but effective treatment. In this treatment, traditionally the pulp tissue will be removed and replaced by the synthesis obturation materials, such as paste or gutta percha.[13,17] RCT aims to remove space for microbiome re-infection and create healing environment by mechanical or chemical disinfection continued by inert material closure.[2,26] The treatment has high success rate in dentistry, which 97% from one million teeth able to functionally retain around eight years span.[13,17]

Tooth which received RCT will experienced severe defect of hard tissue, devitalized pulp from denervation, and avascularity. This will lead to an increased risk of fracture, disruption of pulpal defense mechanisms, and loss of physiological functions such as nutrition and sensory.[2,17,27] To prevent the side effects, an effective treatment strategy is needed for revitalization in pulp treatment. The emergence of tissue engineering technology and regenerative treatment provides possibility for development of regenerative endodontic treatment.[17]

ENDODONTIC REGENERATIVE

The challenge in modern dentistry is to maintain the pulp vitality which implicated from RCT which caused the tooth to be non-vital and susceptible to structural changes.[28] Thus, interdisciplinary approach of regenerative treatment has developed which was utilized living cell to heal, replace, and restore the damage human tissues and organs into their normal functions. One of them is a stem cell engineering which has potential to be the future of regenerative treatment.[29,30]

Dental tissue regeneration could be obtained by the regeneration of each part of tooth structure, which consist of email, dentin, pulp, alveolar bone, cementum, and periodontal ligament, or by regenerating whole tooth structurally and functionally.[15,31] Regenerative

endodontic is one of the endodontic treatments which focus on replacing damage pulp tissue through tissue regeneration to restore the tooth vitality which lead to the increase of patient's quality of life. Regenerative tissue should has healthy pulp's properties, such as ability of dentin deposition process, reinnervation, and vascularization.[17,26]

TISSUE ENGINEERING

Tissue engineering technology is an interdisciplinary science which implemented biological principals' regenerative treatment technique with the focus on repairing and restoring the biological function of cells, tissues, and organs, which injured by the internal or external factors.[6,32] Tissue engineering technology aims for contributing to damage tissue function and structure restoration with the utilization of stem cell interactions, scaffold/biomaterial, and growth factors. Proper combination of these three elements is able to manipulate the biomimetic microenvironment which contains vascularly system which normally function with the nutrition supply, waste disposal, inflammatory response, and next pulp regeneration.[2,6,33] In tissue engineering, angiogenesis has important role, such as in nutrition supply and potential recruitment of stem cell.[4,34]

In tissue engineering technology, pulp regeneration could be achieved by utilization of three key elements, which are (i) stem cell, (ii) scaffold, and (iii) signaling molecules, such as growth factors. At first, pulp regeneration process could be achieved through the stem cell isolation and *in vitro* manipulation. After that, the cells are cultured in the scaffold combined with the growth factor and transplanted into the root canal.[35–37]

Every element will give difference impacts for the pulp regeneration, but all of them will support each other to provide favorable result. Proper combination of these three elements will provide micro biomimetic environment, which influence the pulp regeneration accomplishment. This result could be achieved by the formation of fully functional vascular system. Thus, it would provide adequate nutrition supply, waste disposal, inflammation response, which lead to satisfactory pulp regeneration.[2]

DENTAL STEM CELL

Mesenchymal stem cell (MSC) is a stem cell which suitable for regenerative treatment because of high proliferation and multipotential ability.[29,38] MSC was marked with positive

CD29, CD44, CD73, CD90, CD105, and Stro-1, and negative hematopoietic marker such as CD14, CD34, dan CD45 according to minimal criteria from International Society for Cellular Therapy.[13,39]

MSC could be isolated from different location in oral and maxillofacial region, such as dental pulp stem cells (DPSCs) dan stem cells from human exfoliated deciduous teeth (SHED) which isolated from healthy pulp tissue. These cells could be differentiated *in vitro* into adipocyte, odontoblast, osteoblast, and chondroblast which will form dentin or pulp tissue after transplanted *in vivo*.[13,29] Other cells such as dental follicle progenitor stem cells (DFPCs), periodontal ligament stem cells (PDLSCs), and stem cells from apical papilla (SCAPs) could be differentiated *in vitro* into adipocyte, odontoblast, cementoblast like cell, and connective tissue.[5,13,29,40]

Each of the stem cells have different properties, SHED and SCAP has a higher proliferation activity compared to DPSC. Although, all the stem cells possessed the potential to regenerate dentin and pulp.[5,13]

GROWTH FACTOR

Signaling molecules, such as stem cell factor (SCF), stromal cell derived factor (SDF-1α), Platelet Derived Growth Factor (PDGF), basic Fibroblast Growth Factor (bFGF), and Granulocyte Colony-Stimulating Factor (G-CSF) were be used for pulp tissue regeneration.[17] Several growth factors, such as SDF-1α, bFGF dan PDGF, are chemotaxis molecules and correlated with blood vessels, nerves, and dentin in pulp regeneration process. PDGF and VEGF contributes in vasculogenesis/angiogenesis, while NGF contributes to grow and survival of the nerves, and BMP-7 contributes to differentiation and mineralization odontoblast.[36,37] Growth factors will play roles in stimulation restoration of structure and physiology of tissue function in damaged tissue.[2]

SCAFFOLD

Scaffold is a three-dimensional frame micro-environment which facilitates attachment, cellular infiltration, differentiation, proliferation, and stem cell metabolism with the aid of growth factors. The frame has to provide support to nutrition and oxygen diffusion in

regeneration process and should has biodegradable property because it will be replaced by the new tissue.[4,6,41]

Several type of developed scaffold materials or models has certain flexibility and degradability.[6] Currently, natural or synthetic scaffold start to commonly be used in pulp tissue regeneration.[2] Several scaffolds which could be used were tissue extracts, such as blood clot, platelet rich fibrin (PRF), platelet rich plasma (PRP), tricalcium phosphate ceramic, hydroxyapatite calcium, and mineral trioxide aggregate, synthetic polymer such as polylactic-co-glycolic acid, polylactic acid, and biopolymer such as collagen, hydrogel, hyaluronan, and chitosan.[4]

Blood clot is one type of scaffold which has natural property and derives natural substance such as collagen, chitosan, fibrin, hyaluronic acid, gelatin, alginate, and peptide-based scaffold. These scaffolds had studied as scaffold for pulp regeneration because of the biocompatibility, biomimetic property, availability, cost effective, and easy to convert into hydrogel.[13,42]

Other than natural scaffold, there were several developed synthetic polymers such as polyglycolic acid (PGA), poly(d,l-lactide-coglycolide) (PLGA), polylactic acid (PLA), poly(l-lactic) acid (PLLA), and polycaprolactone (PCL), inorganic calcium phosphate such as hydroxyapatite (HA) or beta tricalcium phosphate (β TCP), and combination of silica glass and phosphate. Synthetic scaffolds had studied considerably as scaffold which have the potential for tooth regeneration, because the un-toxicity, biodegradable, and easy to manipulate properties, including the mechanical rigidity and degradation rate.[2,15,42]

Different with natural scaffolds, synthetic scaffold could be prepared with unlimited number, because it could be produced in controlled environment according to desirable shape. This condition allowed to obtain the scaffold in accordance with cell differentiation properties, certain pore characteristic, and certain mechanical, chemical, and degradation rate properties according to desirable application.[15,43,44]

This polymer is a biomaterial which commonly used to form scaffold with characteristic related with differentiation of composition, structure, and macromolecule arrangement.[15] In recent studies, scaffold has a potential to be bioactive carrier and recapitulate interaction between stem cell, progenitor cell, micro-physiological environment, and extracellular matrix.[13] In the regenerative endodontic treatment, polymer scaffold usage could provide physiological environment to increase the biological performance in pulp regeneration process. This process

consists of re-vascularitation and revitalization process. This scaffold influences the cell migration, viability, discharge, proliferation, recruitment, and degradability.[45]

Although scaffold has huge potential, there are challenge which need to be overcome, which is integrating the scaffold with complicated morphology without damaging surrounding tissue. For tooth regeneration, scaffold required several general requirements, such as easy to manipulate, has bioactive and biodegradable properties, has adequate porosity, physical and mechanical strength, has low immunogenicity, and support of vascularization.[15,43]

Other criteria such as adequate shape, size, and pore's volume are important for penetration and diffusion of growth factors, nutrition, and waste discharge between cells.[13,15] Therefore, scaffold's criteria and design will create favorable micro-environment which are important for the foundation to perform the tissue engineering technology. This micro-environment will support to organize the cell function in self-renewal and differentiation, support the cell dan growth factor transportation, create environment for cell activities, and promote communication between cell which lead to tissue regeneration.[2,13,46] Scaffold characteristics are the important keys to process of tissue regeneration, because it plays a role in defining cell behavior and tissue formation.[13]

To confirm the success of cell growth and differentiation process in tissue engineering, scaffold materials must be able to interact with host tissue and provide ideal environment for tissue growth.[29,46] Ideal scaffold for pulp regeneration should fulfil three criteria, which are biocompatibility, adequate rigidness to withstand mastication force, and provide tight sealing with dentin to prevent microorganism infiltration.[29,44] Other than that, rate of scaffold degradation should be suitable with the rate of new tissue formation and will not produce harmful waste side products.[15,47,48]

NATURAL SCAFFOLD

One of the tissue engineering triads in regenerative endodontic is scaffolds which works as biological and structural support for cell growth and differentiation. Proper scaffolds selection is a challenge in dentin-pulp regeneration process.[49] Cells' migration, proliferation, and differentiation are correlated with choice guide of scaffold's physical properties, such as appropriate viscoelasticity to mimic the real pulp tissue.[50] Application of scaffold for dental pulp

regeneration should be able to mimic the micro-environment in the root canal and provide the mechanical support.[51,52]

Application of 3D bioprinting technology in scaffold can precisely mimic the external and internal morphology. The 3D scaffold has moderate porosity which allows nutrition and oxygen infiltration which leads to occurrence of metabolic activites.[52] Scaffold application through injection process is recommended because it could adapt well with the shape of pulp chamber and root canal so the cell interaction and matrix could occur efficiently.[49]

To current date, scaffolds are classified as natural and synthetic scaffolds, based on the material source and biomaterial properties.[53] Scaffolds for tissue regeneration using natural or synthetic materials are continuing to be developed.[54] Natural scaffolds came from the host or natural materials. The example of host's scaffolds is blood clot, autologous platelet concentrates, and decellularized extracellular matrix.[53] While the example of natural materials scaffolds is collagen, alginate, chitosan, hyaluronic acid, dan fibrin.[49,50,52,53] Scaffold from natural materials have the advantages of ability for cell recognition and adhesion from molecular signaling. Although, the application of this scaffold has the limitation of products' variation, risk of pathogen transmission, and poor mechanical properties and immunological responds to foreign objects.[51] The shape of scaffold could be a porous sponges, solid bocks, sheet, or hydrogels.[55]

Collagen is a scaffold material which has the closest viscoelasticity to real pulp tissue.[50] The combination of natural materials such as collagen and host's blood clot showed predictable pattern for tissue formation and mineralization in human dental, compared with individual collagen or blood clot. Application of one type of scaffold, such as blood clot will not provide stable result for tissue regeneration process.[56] Instability and unpredictable clinical result from the blood clot are the consequences from unregulated stem cell in pulp chambers, including the difficulties of bleeding formation and hemostasis.[51]

Compared with blood clot, Platelet Rich Plasma (PRP) dan Platelet Rich Fibrin (PRF) provided lower results in the increase of dental root length and less effectivity in root development.[57] PRP from the host blood contain high platelet, growth factors, and cytokine concentrations, which increase the ability of wound healing, stem cell recruitment from the pulp, and increase SCAP proliferation. While PRF contains plentiful of growth factors which could stimulate the cell differentiation, beside cell adhesion and migration.[58] The advantages of materials with rich platelet concentration such as PRF or PRP are increase of angiogenesis and

revascularization level, which is the fundamental of accomplishment of endodontic regeneration therapy.[55] Hydrogel based collagen could mimics the interaction between cells and extracellular matrix *in vivo* and organized the cell growth which used for tissue engineering.[59]

Polymer materials such as gelatin and fibrin commonly used as natural scaffolds. Gelatin is a biopolymer protein come from the collagen hydrolysis which could facilitate the proliferation and differentiation of odontoblast in dental pulp stem cells (DPSCs).[49] Gelatin is a partial hydrolysate from animals. Compared with gelatin, hydrogel gelatin has better biocompatibility because of the low immunogenicity properties.[49,52] Gelatin based matrix showed better endodontic therapy result compared with fibrin-based matrix groups after 12 weeks follow up in minipig immature dental models.[49]

Other studies of fibrin-based scaffolds in hydrogel form, showed that this material was compatible with dental pulp regeneration by supporting pulp-like tissue formation.[60] Fibrin is a natural protein polymer which is a part of blood clot formation. Hydrogels based fibrin can stimulate pulp-like tissue formation with odontoblast layer in root canals system.[49] The advantages of these materials are the good cytocompatibility, physical kinetic degradation, and non-toxic degradation products, which also easy to inject in the pulp canal. Other natural materials (such as alginate, chitosan, collagen, hyaluronic acid) or synthetic materials (such as polyethylene glycol, poly (D,L) lactic acid, and fibrin based bio-ink 3D printing) were added to increase the structural and functional properties of fibrin scaffold.[60]

Alginate is a natural polymer from algae with good biocompatibility properties, cost effective, low cytotoxicity, and has optimal structure for nutrition exchange.[45,51,52] Alginate hydrogels were formed by polysaccharide and divalent cations crosslinking to form ion bridge in water insoluble tissue.[51] Alginate hydrogels are able to arrange in accordance with the mechanical properties such as rigidity and stress relaxation to regulate the stem cell activity.[45] Alginate has proper mechanical properties, but can be applied in hydrogel injection form or bone porosity which enable the natural structure to be loaded of growth factor.[55] Macroporosity of alginate scaffolds were enabled the nutrition and metabolism waste exchange. But scaffold which consists of alginate only has limited roles in endodontic regenerative therapy, therefore combination with other materials such as bioactive polymers is needed.[51]

Hyaluronic acid (HA) is a biopolymer which could be modified and processed for biomedical application and combined with other materials to increase the favorable properties.[59] HA was

found in dental pulp and decrease through dental development in odontogenesis process.[51] When applied to exposed pulp, HA could stimulate the production of reparative dentin. HA could be applied in 3D sponge form to create proper environment for blood vessels proliferation and stem cell differentiation.[55] HA is formed by d-glucuronic acid dan N-acetyl-D-glucosamine, and commonly available in injection liquid.[45] HA degradation products include pro-angiogenic growth factors which are the revascularization elements for dental regeneration tissue. Although HA has disadvantages of poor mechanical properties and can cause hypersensitivity reactions.[51]

Chitosan is a widely used natural scaffold.[61] Chitosan is a cation polymer from chitin.[54] Chitosan has good biocompatibility, biodegradation ability, and other favorable biological properties such as antimicrobial, fungistatic, hemostatic ability, non-carcinogenic, protein fusion ability, and stimulate the cell adhesion, proliferation, and differentiation ability.[54,61] Although, the application of chitosan is difficult because of the complex gelation and degradation scheme process because of unusual polycationic and high crystalline structure which limit the scaffold application in the natural injection form.[51] Hydrogel form of chitosan can be injected to the dental pulp chamber.[61] Chitosan can be applied as individual scaffold or in combination with polymer or other biomaterials to produce large number or matrices for tissue engineering purposes. Addition of chitosan scaffolds in blood for endodontic regeneration procedure can stimulate the formation or new soft tissue which proven by the histological regeneration, without the formation of mineralized tissue around the pulp canal wall.[54] The result of photo-biomodulation therapy addition could increase the *in vitro* stem cell survival, proliferation, and migration from root papilla.[61]

Between several natural scaffold, other studies showed that human tooth can be applied as scaffolds for periodontal ligament and pulp regeneration.[26] Scaffolds from natural materials have higher biocompatibility and bioactivity properties compare with synthetic scaffolds. While synthetic scaffolds have higher controlled degradation level and mechanical properties.[62] The application of scaffolds not only limited to one material but can be combined for better endodontic regeneration therapy.

SYNTHETIC SCAFFOLD

The implantation of 3D scaffold in the appropriate living cells that secrete their own extracellular matrix (ECM) can provide an acceptable environment. Adequate porosity and

permeability of polymeric scaffold is essential to guide and support the cultured cells' ability to produce tissue. Synthesizing synthetic biodegradable polymers are challenging in tissue engineering applications.[63,64]

The progenitor/stem cells should then be able to attach, travel through, proliferate, organize themselves spatially in 3D, and differentiate into the odontogenic, vasculogenic, and neurogenic lineages with the support of an adequate scaffold for dentin pulp regeneration. Furthermore, the biocompatibility of the material is critical to avoid any negative reactions from the host tissue. A biodegradability that can be adjusted to match the rate of regeneration is critical for facilitating constructive remodeling. As a result of scaffold deterioration, a series of tissue responses occur, comprising target tissue replacement of the scaffold, vascularization, differentiation, spatial structure, and cellular infiltration.[65–67]

Metals, ceramics, and polymers are the example of the materials that can be used to make scaffolds. Both dental and bone implants are frequently made of metallic alloys. When it comes to bone tissue engineering, ceramics with strong osteo-conductivity have been used. Although, metals and ceramics have substantial disadvantages because metals do not biodegrade and do not serve as a matrix that mimics biological processes for the proliferation of cell and tissue creation. Additionally, due to its brittleness, ceramics are difficult to convert into highly porous structures and have a limited capacity for biodegradation. In contrast, polymers can be molecularly designed to have increased biodegradability and excellent processing flexibility. So, in tissue engineering, polymers are the most common type of scaffolding material.[31,67–69]

Biological recognition is a potential benefit of naturally generated polymers that may help to stabilize cell adherence and work properly. The synthetic polymers used as scaffolding materials have been spurred by the challenges associated with natural polymeric materials, such as their complex purification, structural composition, pathogen transmission, and immunogenicity. When compared to naturally occurring extracellular matrix (ECM) proteins, synthetic polymers offer better processing flexibility and no immunological issues. Functionalized scaffolds that combine the benefits of synthetic and natural polymeric materials can be made by adding bioactive molecules to synthetic polymers.[68–70]

Synthetic polymers’ advantages include nontoxicity, biodegradability, and the ability to precisely manipulate physicochemical characteristics such as degradation rate, structural rigidity, microstructure, and porosity.[71–73] Natural polymers are mostly broken down by enzymes, but

synthetic polymers are typically broken down by simple hydrolysis. However, because of the relative acidity of the hydrolytically destroyed byproducts, synthetic polymers might cause localized pH reduction and a chronic or acute inflammatory host response.[73–75]

Tissue engineering frequently uses poly (-hydroxy acids), such as poly (lactic acid), poly (l-lactic acid), poly (glycolic acid), polyethylene glycol, and their copolymer poly [(lactic acid)-co-(glycolic acid)] (PLGA), and polyepsilon caprolactone (PCL), which appears to be the most synthetic polymeric materials. These polymers have an established track record and have been approved by the FDA for specific human applications (e.g., sutures). Two of the synthetic polymer scaffolds that have been suggested for dental tissue engineering are PGA and PLA, which are biodegradable polyesters that can be produced from a range of renewable sources. Compared to PGA, PLA, an aliphatic polyester, is more hydrophobic.[65,68,73,75–77]

The synthetic scaffold known as PGA, which has been used for cell transplantation, breaks down when the cells secrete ECM. Several cell types, including cellular origins of dental pulp, pulpal fibroblasts, and ex vivo human pulp tissue cells, have been shown to be able to adhere and develop on PGA scaffolds. Copolymers of PGA and PLA sown with dental pulp progenitor cells have been shown in rabbit and mouse xenograft models to produce pulp-like tissue.[65,68,73,74]

Since structural strength is vital in many applications, PLLA, an extremely strong polymer, has been used in several of them. Nano-fibrous scaffolds have been created from it to resemble the structure of genuine collagen (a crucial element of ECM). It has been shown that the nano fiber PLLA scaffolds promote cell attachment and differentiation. According to previous studies demonstrating how PLLA scaffolds stimulated the development of endothelial cells from dental pulp cells and odontoblasts.[65,68,74] It was demonstrated utilizing PLGA as a scaffold that dentin-like tissue could emerge, and that pulp-like tissue could be repaired over the course of three to four months. A 50:50 blend of PLGA degrades after around 8 weeks. PCL, a slowly disintegrating polymer, has been utilized in bone tissue engineering projects either by itself or in conjunction with hydroxyapatite.[74]

A different type of polymer, polyethylene glycol, is utilized in tissue engineering techniques, such as pulp regeneration. Dental pulp progenitor cells have been transformed to create 3D tissue constructs while being linked to electro spun polyethylene glycol scaffolds. These artificial polymer scaffolds have also been utilized to convey a range of substances, including anti-inflammatory drugs, growth hormones, and sticky proteins. Such scaffolds could not only

support cell growth and proliferation but also reduce pulpitis and aid in pulpal healing. Synthetic polymer scaffolds have better handling characteristics and a more straightforward manufacturing process, which improves their potential for endodontic regeneration. They do, nevertheless, differ significantly from the natural the dental pulp's extracellular environment. As a result, ECM-based natural scaffolds that are more close to the microenvironment have been developed.[65,73,78,79]

Planting human exfoliated deciduous teeth stem cells (SHED) on dentin disks with PLA resulted in the structure of odontoblast-like cells, new dentin, and vascularized pulp-like tissue. Study by Huang et al. illustrated that when implanted *in vivo* into an empty root canal area, constructions of stem cells from the apical papilla (SCAPs) and L-lactide, poly-D, and glycoside have been shown to be able to create soft tissue that resembles pulp and the continual addition of new dentin to the surface. However, synthetic polymers have the potential to cause an immediate or long-lasting inflammatory response. Additionally, the locally decreased pH brought on by the hydrolytically degraded metabolites may impair the clinical use.[65,74]

Several methods have been used to construct 3D scaffolds from poly (hydroxyacids). The inability of the poly(a-hydroxyacids) chains to allow functional groups, however, restricts the incorporation of biologically active moieties onto the scaffolding surface. To increase the functioning of these polymers and broaden their uses, significant efforts have been made in this direction. Creating copolymers out of a-hydroxy acids with additional monomers that have functional pendant groups, including amino and carboxyl groups, is one technique. In one study, ring-opening polymerization was used to copolymerize (RS)-b-benzyl malate and L-lactide, then the benzyl groups were removed to create (RS)-b-malic acid) poly (L-lactide) with connected carbonyl compounds.[68,80,81]

To copolymerize with L-lactide, benzyloxymethyl methyl glycolide and benzyloxymethyl glycolide are required which have preserved hydroxyl groups. The matching hydroxylated PLLA copolymers were produced when the benzyloxymethyl groups were deprotected. Comparable carboxylic acid functionalized copolymers are created using succinic anhydride.[68,82]

The researchers created a poly [(L-lactic acid)-co-(L-lysine)] containing a useful lysine residue that there further linked to the RGD peptide. Even though the development of functional groups in random copolymers by lactide/glycolide copolymerization with additional monomers is successful, this procedure frequently affects the physical characteristics of the starting

homopolymers (such as crystallinity and mechanical strength). Numerous block and graft copolymers based on poly(a-hydroxyacid) have been developed and made as a result of this.[68,83]

Polymers' PEG, or poly (ethylene glycol), is the component that most frequently used (a-hydroxyacids). PL(G)A/PEG diblock, triblock, and multiblock copolymers could be made by the ring-opening of PEG and certain catalysts, and presence of glycolide/lactide polymerizes. However, the hydroxyl or carboxyl (functional groups) in the block copolymers containing PEG are only present at the end of each PEG segment, and the content in these block copolymers is very low, restricting further chemical alterations. Numerous block and graft copolymers made without PEG have been described.[68,84]

Amphiphilic poly [hydroxyalkyl (meth) acrylate)] is a variety of biodegradable polymers. Copolymers of -graft-poly (L-lactic acid) (PHAA-gPLLA) with hanging hydroxyl groups were employed to successfully produce 3D nano-fibrous scaffolds. Further functionalization of these copolymers can result in biomimetic scaffolds that are more hydrophilic, degrade more quickly, and have uses in tissue engineering.[68,85]

Fabrication of highly porous scaffolds poly (α-hydroxyacid) for tissue engineering based on star-shaped functional poly(ε-caprolactone). Functional groups were added to PCL chains using similar methods. The example of these methods is the copolymerization of ε-caprolactone and a-chloro-ε-caprolactone to produce functionalized PCL copolymers, and the subsequent addition of carboxyl, pendant hydroxyl, and epoxide groups via atom transfer radical addition. In order to produce the pendant hydroxyl groups in the PCL copolymers, ε-caprolactone was copolymerized with another monomer, 5-ethyleneketal-ε-caprolactone, and the resulting molecule was subsequently deacetylated to convert the ketone groups into hydroxyl groups.[68,86]

However, the de-protection processes as well as the synthesis of these functional comonomers are typically challenging and time-consuming. Aside from poly(3-hydroxybutyrate), polyurethanes, polycarbonate, poly (ortho ester), poly (propylene fumarate), and polyphosphazenes, other synthetic biodegradable polymers have also been applied as scaffolding biomaterials. Comparatively to the polymer, there are much less reports of functionalizing these biomaterials (a-hydroxy acids) which includes the creation of functionalized PC using synthetic methods.[68,86,87]

Pendant amino groups were added to PC chains after polymerizing the cyclic carbonate monomer (2-oxo-[1,3]-dioxan-5-yl) carbamic acid benzyl ester and getting rid of the protective

benzyloxy carbonyl groups. The pendant amino groups' further functionalization was shown using RGD peptide grafting. The synthetic efficiency should be considered given the number of steps in this reaction cycle.[68,88]

The five distinctive structural characteristics of these PAs are as follows: (1) possess an extended alkyl tail that contributes to the molecule's amphiphilic characteristic; (2) to maintain the structure, possess four consecutive cysteine residues that create disulfide bonds; (3) possess a flexible hydrophilic head group due to the three glycine residues in the linker region, which separates the hard cross-linked region; (4) contain phosphorylated serine residues that interact strongly with calcium ions to encourage mineralization; and (5) contain an effective RGD peptide.[68]

The high electrostatic interaction between molecules causes the PAs to self-assemble into nano-fibrous networks when the pH is changed or divalent ions are added, as evidenced by this study. Additionally, the hydrophilic peptide signals can be displayed in a specific way on the surfaces of the produced nanostructures due to the molecules' amphiphilic characteristics. However, the creation of sufficient mechanical three-dimensional from these PAs must be addressed, just like with several other hydrogel materials. Proteinase-sensitive motifs are an inventive technique to make biomaterials react to cells.[68,89]

As cell-ingrowth frameworks for tissue formation, Hubbell et al. presented a valuable example of how to build synthetic PEG-based hydrogels. Functionalization molecules for PEG chains in the hydrogel networks that also include pendant oligo peptides (RGDSP) for cell attachment are matrix metalloproteinase (MMP)-sensitive peptides. The material's reaction to MMPs secreted by cells is controlled by the MMP-sensitive binding agent. This hydrogel with a PEG foundation functions as a biomaterial and reacts to cells. The authors also shown that these gels can promote bone regeneration and are efficient delivery systems for recombinant human bone morphogenetic protein-2 (rhBMP-2).[48,68]

Many of the requirements of dental pulp tissue engineering approach may be accommodated by self-assemble, adaptable, and customizable peptide. Due to the peptide chains' natural amino acid makeup, it can produce biodegradable products. The potential for uniform cell encapsulation, rapid transport of nutrients and metabolites, and the characteristics of peptides hydrogel systems include their viscoelastic properties, which are comparable to the properties of collagenous tissues like dental pulp.[65,90]

The term "bioceramic scaffolds" refers to a group of materials that includes glass ceramics, bioactive glasses, and calcium/phosphate compounds. Calcium phosphate-based (CaP) ceramics are the biomaterials that are utilized the most frequently. Due to their characteristics of osteoclast genesis, nontoxicity, antigenicity, osteoinduction, bone bonding, and similarity to mineralized tissues, CaP scaffolds, such as -TCP or HA, have been extensively explored for bone regeneration. 3D CaP porous granules have demonstrated potential in the engineering of dental tissue by providing excellent 3D substrate characteristics for hDPSC growth and odontogenic differentiation. Pure TCP scaffolds are doped with SiO2 and ZnO to increase their mechanical stability and capacity for cellular proliferation. Glass ceramics made of SiO2 Na2OCaOP2O5 are bioactive and offer ideal crystallization conditions. Osteoblastic activity of the substance is increased by the release of dissolving products such CaP.[15,74]

Ceramic scaffolds can be altered to control dissolving rate, provide the appropriate permeability, and certain surface properties to promote cellular activity. The mechanical rigidity of the scaffold is influenced by variations in pore size and volume. Glass ceramics made of magnesium have increased mechanical strength and a high rate of bioactivity. Excellent hDPSC attachment, proliferation, and differentiation are showed in niobium-doped fluorapatite glass ceramic.[74,91]

Several disadvantages of bioceramics include longer time to make, lack of organic phase, have nonhomogeneous particle size and form, huge grains, difficult to shape, brittle, degrade slowly, and have a high density. The bioceramics are fragile and have little mechanical strength when individually utilized. This drawback can be remedied by combining them with polymer scaffolds.[74,91]

CONCLUSION

Various types of scaffolds, both natural and synthetic, can be used to regenerate dental pulp by utilizing tissue engineering technology. Scaffolds made from natural materials have advantages in cell recognition and molecular signal adhesion, while synthetic scaffolds can be made in unlimited quantities. However, it will give a better effect if the two types of scaffolds are combined to obtain good mechanical properties so that they can support pulp regeneration properly.

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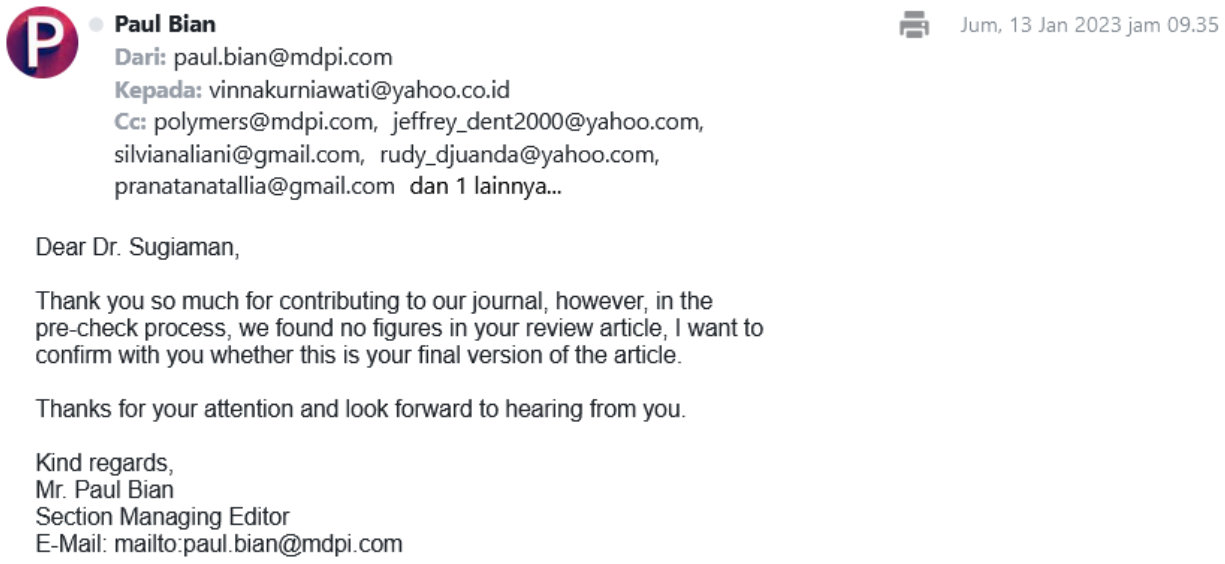
Bukti melakukan review yang pertama (13 Januari 2023)



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Cc: polymers@mdpi.com, jeffrey_dent2000@yahoo.com, silvianaliani@gmail.com, rudy_djuanda@yahoo.com, pranatanatallia@gmail.com dan 1 lainnya...

Jum, 13 Jan 2023 jam 09.35

Dear Dr. Sugiaman,

Thank you so much for contributing to our journal, however, in the pre-check process, we found no figures in your review article, I want to confirm with you whether this is your final version of the article.

Thanks for your attention and look forward to hearing from you.

Kind regards,
Mr. Paul Bian
Section Managing Editor
E-Mail: mailto:paul.bian@mdpi.com

Bukti konfirmasi submit revisi pertama yang telah direvisi (26 Januari 2023)

Vinna Kurniawati Kam, 26 Jan 2023 jam 08.27
Dari: vinnakurniawati@yahoo.co.id
Kepada: Paul Bian
Cc: parasca@mdpi.com

Dear,
Mr. Paul Bian and Ms. Denisa Parasca

Here I attached figures and tables that are planned to be included in our article. Thank you.

Yours sincerely,

Vinna. KS
Pada Jumat, 13 Januari 2023 16.21.52 GMT+7, vinnakurniawati <vinnakurniawati@yahoo.co.id> menulis:

Ok... thank you

Bukti melakukan review yang kedua (30 Januari 2023)

Please revise the manuscript according to the referees' comments and upload the revised file within 10 days.

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(I) Please check that all references are relevant to the contents of the manuscript.
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Polymers Editorial Office
Dari: polymers@mdpi.com
Kepada: Vinna Kurniawati Sugiaman
Cc: Jeffrey Jeffrey, Silvia Naliani, Natallia Pranata, Rudy Djuanda, Rosalina Intan Saputri dan 1 lainnya...

Rab, 8 Feb 2023 jam 16.15

Dear Dr. Sugiaman,

Thank you very much for providing the revised version of your paper:

Manuscript ID: polymers-2180284
Type of manuscript: Review
Title: Application Polymeric Scaffolds for Dental Pulp Regeneration With Tissue Engineering Approach.
Authors: Vinna K Sugiaman *, Jeffrey Jeffrey, Silvia Naliani, Natallia Pranata, Rudy Djuanda, Rosalina Intan Saputri
Received: 8 January 2023
E-mails: vinnakurniawati@yahoo.co.id, jeffrey_dent2000@yahoo.com, silvianaliani@gmail.com, pranatanatallia@gmail.com, rudy_djuanda@yahoo.com, rosalina.is@dent.maranatha.edu

We will continue processing your paper and will keep you informed about the status of your submission.

Kind regards,
Ms. Denisa Parasca
Assistant Editor
MDPI Open Access Publishing Romania
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Bukti konfirmasi artikel diterima (18 Februari 2023)

Polymers Editorial Office
Dari: polymers@mdpi.com
Kepada: Vinna Kurniawati Sugiaman
Cc: Jeffrey Jeffrey, Silvia Naliani, Natallia Pranata, Rudy Djuanda, Rosalina Intan Saputri dan 2 lainnya...

Sab, 18 Feb 2023 jam 13.27

Dear Dr. Sugiaman,

Congratulations on the acceptance of your manuscript, and thank you for submitting your work to Polymers:

Manuscript ID: polymers-2180284
Type of manuscript: Review
Title: Application Polymeric Scaffolds for Dental Pulp Regeneration With Tissue Engineering Approach.
Authors: Vinna K Sugiaman *, Jeffrey Jeffrey, Silvia Naliani, Natallia Pranata, Rudy Djuanda, Rosalina Intan Saputri
Received: 8 January 2023
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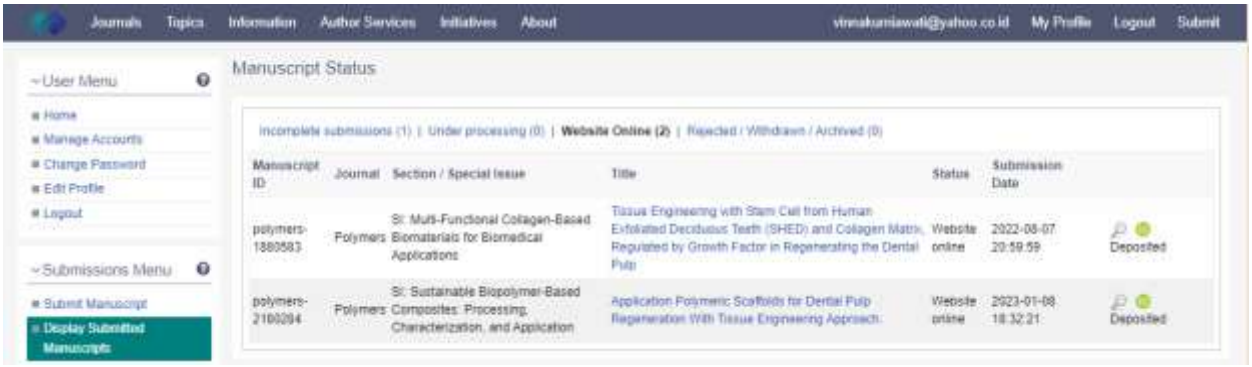

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