Review │ Received 30 April 2024; Accepted 4 June 2024; Published XX June 2024
https://doi.org/10.55092/bm20240003

Biofunctional materials for dental disorders

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Abstract: Dental treatments are currently based on conservative approaches, using inorganic materials and related appliances. Biomaterials including both natural/chemical play a vital role in dental tissue engineering. Biomaterials are utilized for fabricating frameworks known as scaffolds, matrices, or constructs to afford optimal dental tissue regeneration. The identification/utilization and development of appropriate biomaterials to optimize and regenerate these hybrid dental tissues is a greater challenge for dental researchers. Biomaterials are tailored to offer good interconnected porosity, large surface area, mechanical strengths, varying surface characterization, and different geometries for effective dental tissue regeneration. A literature search was made on articles, which are available in Pubmed, using key searches, such as biomaterials, tissue regeneration, tissue engineering, regenerative dentistry, periodontal regeneration, and hard/soft dental tissue regeneration. Papers were mostly searched from 2000 onward. In this review paper, we discussed about dental diseases, applications, and tissue engineering strategies in dentistry, biomaterials used in tissue engineering for tooth regeneration, bone regeneration, enamel regeneration, periodontal tissue regeneration, oral mucosa regeneration, salivary gland regeneration, and dentin/dental pulp regeneration.

Keywords: tissue regeneration; dental; biomaterials; tooth

1. Introduction

Oral diseases are the most prevalent noncommunicable diseases which may cause lifetime discomfort, pain, and even death. The most common cause of orofacial pain is associated with dental disease. Critical assessment, diagnosis, management, and treatment play a vital role towards dental management. Periodontitis is caused due to infectious inflammation of the teeth. Periodontitis severity leads to connective tissue and dental bone destruction.

Children and adolescents are prone to several forms of periodontitis such as aggressive periodontitis, chronic periodontitis, and periodontitis-associated systemic diseases [1,2]. At most 5–20% of tooth loss is caused due to periodontitis. Periodontitis may lead to the cardiac/cerebrovascular/arterial/neonatal disorders. These may be achieved by infection spread from the oral cavity, and metastatic injury from multifactorial mechanisms. The destructive mechanism of periodontitis includes direct/indirect tissue damage through bacterial induction of the host's inflammatory and immune responses [2].

The missing alveolar bone during tooth extraction and overall ridge profile over long periods of edentulous individuals are the causes of tissue damage. Clinical investigations suggest that hard/soft tissue defects occur due to traumatic tooth extraction. The condition of loss of supporting periodontal and surrounding teeth bone during the conditions of apical periodontitis may also result in tissue damage. Hard tissue deficiencies may occur due to longitudinal root fractures which may lead to bone resorption [3]. The alteration in the intra-ocular pressure may lead to trauma. The abnormal/ incomplete tooth and bone formation during various phases like ectodermal dysplasia are associated with systemic diseases.

Plaque accumulation, calculus formation, gingival redness/swelling/bleeding, and suppuration are the major reasons for tissue loss. Poor oral hygiene, smoking or chewing tobacco, genetics, crooked teeth that are hard to keep clean, pregnancy, diabetes, and medications (steroids, anti-epilepsy drugs, cancer therapy drugs, calcium channel blockers, and oral contraceptives) are the various factors influencing. The periodontal treatment, such as rooting and scaling, by removing plaque at the root of the teeth and reducing inflammation The progression of periodontal disease may be slowed by utilizing various approaches. The global 11th most prevalent disease as indicated by the World Health Organization (WHO) has been commenced. Dental treatments are found to be biological.

Replacement of non-functioning tissue by the usage of specific biomaterials will nurture the development of a functionally acceptable regenerated tissue [5]. The damaged tissue replacement may be achieved by bioactive, biodegradable synthetic or natural scaffolds. USCDCP (United States Centers for Disease Control and Prevention) reports that 50% of Americans are prone to periodontal disease. Researchers had developed nanofibrous poly (ε-caprolactone) membranes coated with polydopamine to sticky protein mimicking the utilized muscles which leads towards the involvement of major ions, and encounters with bone mineralization. Further, they checked by implanting the membrane into the rat gums and observed the bone regenerated to normal levels within eight weeks.

2. Dental disorders

2.1 Tooth regeneration

The major involvement of epithelial and mesenchymal tissues in association with the hair follicles and exocrine glands (mammary/sweat/salivary) occurs. Tooth loss may be overcome by conservative therapies. The tissue engineering approach during tooth regeneration coupled with biological processes of healing associated with the repair affords a natural healing potential of the damaged dental tissues thereby supporting the regeneration of the damaged

dental tissue. Ameloblasts are responsible for the enamel formation therefore the mature tooth lacks enamel. Tooth loss occurring due to enamel degeneration may be healed by acellular remineralization (fluoride/calcium phosphate nanocrystals) [6]. Dental pulp stem cells producing dentine have the capacity to repair damaged dental tissues. Exposed pulpal injuries are prone to microorganisms from the oral cavity; thereby dentine cannot be removed before biomaterial application, whereas direct capping of dental pulp may end with necrosis therefore tooth regeneration therapy is recommended. Bio-tooth engineering potentially may hold a greater impact in the field of regenerative medicine. In the case of whole-tooth bioengineering tooth development at the early stage cause the epithelium first to induce tooth formation in the mesenchyme followed by a reciprocal induction from mesenchyme to epithelium. Previous studies reported that epithelium and mesenchyme tissues from E14.5 to E12.5 stage mouse tooth germ cells get dissociated and recombined to form normal teeth [7]. Cellular arrangement in tissue plays an essential role in the organogenesis of tooth development which causes the dental cells to change in its shape/size dynamically. The non-cytotoxic calcium phosphate cements are used as bone substitutes.

2.2 Bone regeneration

During the remodeling of the skeleton with optimal mechanical integrity the osteoclasts and osteoblasts formation occurs. The alveolar bone may get altered due to periodontal disease thereby the surrounding tooth-supporting tissues get destroyed, which leads to the necessitating of tooth extraction. Majorly bone defects occur due to Trauma and other associated infections. The coral, porcine, or bovine-based xenografts offer their role in bone replacement in dental regeneration. Biocompatible and biodegradable organic (Collagen type I, alginate) and inorganic (hydroxyapatite) components are widely used in bone regeneration. The osseointegration rate may be improved by calcium phosphate derivatives. Thermoresponsive copolymer (PEGylated poly(lactic-co-glycolic acid)) was used for osseous defects [8]. Bone marrow mesenchymal cells possess the capacity to respond to odontogenic signals from the epithelium, thereby inducing tooth formation by receiving epithelial signals [9]. Mesenchymal stem cells hold the potential to differentiate into osteoblasts or odontoblasts, with the ability to modulate systematic immunity [10]. In cell transplantation/scaffolds for dental bone tissue engineering the natural materials and synthetic polymers are widely used to support mechanical properties and to afford degradation effect [11]. Bioactive glasses have the capacity to produce bioactive hydroxyapatite upon interaction with biological fluid thereby bonding with biological tissue which may improve differentiation and osteogenesis because thereby activates gene transduction pathways. Calcium phosphate-based salts are majorly present in Dentin. Most of the growth factors are present in the demineralized dentin matrix which may support the osteogenic potential [12]. The dentin formation was supported by the majority of the bioactive molecules present in the dentin matrix.

A novel calcium phosphate cement incorporated gold nanoparticles was developed by Yang Xia *et al.*; 2018 to screen the osteogenic induction ability of human dental pulp stem

cells. The effective cell adhesion was afforded due to the presence of gold nanoparticles which improves human dental pulp stem cells' behavior on calcium phosphate cement. This may cause effective cell adhesion/proliferation/osteogenic differentiation with higher folds [13]. Scaffolds involving different ranges of alginates synergistically with hydroxyapatite nanoparticles have been reported by Abeer Barakat *et al.* for bone regeneration this elicits complete degradation of the scaffolds within 14 to 21 days [14].

2.3 Enamel regeneration

Enamel is composed of crystalline calcium phosphate (96%) and organic components (4%). The major enamel protein amelogenin is the organic content of enamel. Enamel may be transformed from the nano level to the micro level. The presence of hydroxyapatite (HA) crystals grew at the C-axis of the enamel with three structural components. Due to the involvement of aligned crystallites Rods are observed to be the main component of enamel. Next to this interrod enamel is secondary to the enamel matrix. Aprismatic enamel is the third component containing HA crystals. The outermost covering of teeth is the Enamel with nanostructured material with a higher amount of ameloblasts that comprise the tooth. Fluoride-based dental formulations may deform the enamel caries and regenerate enamel [15,16].

2.4 Periodontal tissue regeneration

The gum disease encompasses gingivitis and periodontitis. Periodontitis occurs due to plaques, bacterial dysbiosis, periodontal pockets, gum recession, tissue destruction, and alveolar bone loss. The prevalence of Periodontitis in the United States of America has been reported with a high prevalence based on oral health examinations; with adults over the age of 30 (47%) and increases at the age of 65 (70%) [17]. To prevent migration and to promote regeneration various clinical techniques are adopted. Specific tissue regeneration techniques are utilized to create a three-dimensional space between the defect and root/bone. The 3D complex cell sheet composed of a bone ligament was fabricated by Resmi Raju *et al.*; 2020 by layering periodontal ligament (PDL) cells and osteoblast-like cells on a temperature-responsive system. The bone-ligament structure gets regenerated due to the complex cell sheet group. For large-scale tissue injury, the 3D tissue regeneration tool may be the better choice [18].

2.5 Oral mucosa regeneration

The exogenous substances and pathogens may be prevented by a barrier to the oral mucosa. Tumor resection, trauma, and chronic diseases lead to the loss of oral mucosa. Oral mucosa may be regenerated by integrated biological and bioengineering approaches to simulate the anatomy/physiology of oral mucosa which favors the clinical application by replacing soft tissue defects in the oral cavity. In order to overcome the shortage of oral mucosa by surgeons oral mucosal regeneration plays a pivotal role. The oral mucosal regeneration is supported due to the combined role of oral mucosa stem/progenitor cells and their associated supporters. Oral mucosal regeneration scaffolds include both synthetic and natural materials.

Biocompatible collagen is utilized for oral mucosal regeneration. Collagen as a scaffold also supports wound healing. The biocompatible and economical human fibrin in association with wound healing properties is also used as oral mucosal regeneration biomaterial. The water soluble hypoallergenic homeostatic macromolecule hyaluronic acid supports oral mucosal regeneration [19].

2.6 Salivary gland regeneration

The saliva-secreting acinar (80%) and saliva transporting ductal cells comprise the Salivary gland. Upon direct/indirect exposure to radiations, damage may occur to the salivary gland and its associated epithelial cells, blood vessels, and nerves leading to acute saliva loss. The salivary gland hypofunction leads to Sjogren's syndrome, granulomatous diseases, cystic fibrosis, diabetes mellitus, infections, thyroid imbalance, and liver disease. Saliva secretion may be improved by saliva substitutes and saliva-stimulating agents [20]. In order to regenerate a fully functional salivary gland the organ germ method has been reported [21]. By seeding cells on a 3D scaffold, the artificial salivary gland may be developed. In order to form spheroid structures hyaluronic acid-based hydrogels may be utilized [22]. Direct transplantation of highly homogeneous mesenchymal stem cells on salivary gland regeneration upon irradiation has been reported by Lim *et al.* and they observed high saliva flow rate and salivary gland function improvement. They confirmed that mesenchymal stem cells may regenerate/preserve salivary gland function with improved microvessel density [23]. In 2019, Ji Won Kim *et al.* reported that local delivery of adipose-derived mesenchymal stem cells might regenerate SG damage induced by radioiodine [24].

2.7 Dentin and dental pulp regeneration

Blood into the root canal may observed during the regeneration of dental pulp tissue. For revascularization, or reestablishment of root development better understanding of the vascular network is essential [25]. Stem/progenitor cells, scaffolds, and biomolecules are utilized for dental pulp regeneration. The disinfection process coupled with chemical irrigation affords regenerative endodontic procedures. Collagen-based biodegradable materials are widely used for dental pulp regeneration. Growth factors supporting angiogenesis and promoting blood vessel formation are utilized during dental pulp regeneration.

The incorporation of dental pulp-derived stem cells with bioactive factors in the scaffold was suggested by Kerstin M. Galler *et al.*; 2012 thereby the cell proliferation and angiogenic cascade may be enhanced [26–29]. The different strategies adopted for dental tissue regeneration are shown in Figure 1.

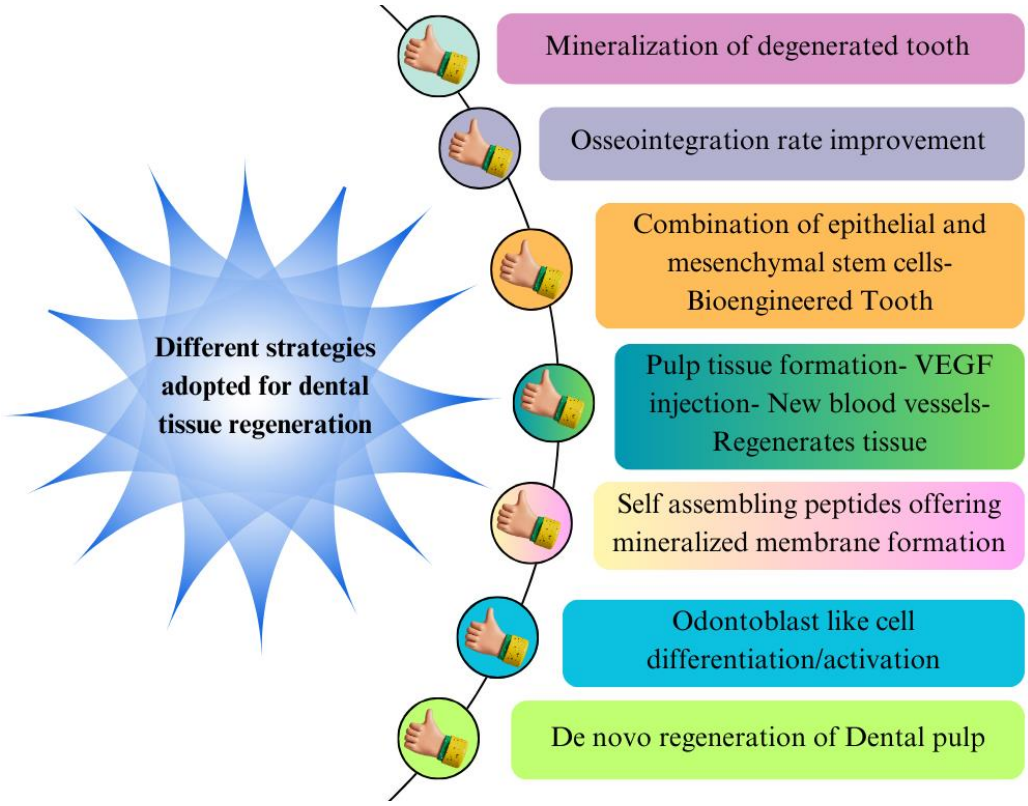

Figure 1. Different strategies adopted for dental tissue regeneration.

3. Applications and Tissue engineering strategies in dentistry

In dental products research the requirement to replace damaged tissue is one of the major challenges. The regeneration of alveolar bone, periodontal ligament, enamel, dentin, and even the whole tooth forms Dental tissue regeneration. The biomaterial design has paved way for the tissue engineering [30]. The serious physiological and psychological consequences cause tissue loss [5]. Whole tissue grafts with the involvement of bioactive, biodegradable synthetic or natural scaffolds combined with cells and/or biological molecules play a vital role in the functional replacement of diseased/damaged dental tissue. Cell injection, cell induction, and cell-seeded scaffold are the tissue engineering strategies utilized for dentistry. Cell injection of intelligent/stem cells results in tissue formation and affords tissues to get regenerated. Challenges involved in cell injection include phenotype maintenance and immunological rejection. Cell induction therapy recruits circulating body cells to regenerate dental tissue. Whereas, osteoinduction using osteoconductive material regenerate damaged dental tissues. Injection of signaling molecules such as growth/differentiation factors (fibroblasts growth factors 2 and 9, transforming growth factors b1, vascular endothelial growth factors, recombinant human growth/differentiation factor-5, and bone morphogenetic protein) regenerates the damaged dental tissues. The isolation of the biopsy cell population (mesenchymal stem cells) from donors forms the potential cell source for tissue regeneration therapies involving wound repair and inflammatory conditions. These constructs support the physicochemical and mechanical maintenance towards the formation of extracellular matrix (ECM) with the properties of slow degradation, resorption, or metabolism upon *in vivo* implantation. The functionality of ECM depends upon the porosity/pore size and structural

interconnectivity. Here open and interconnected pores will support the matrix formation by allowing the growth, proliferation, and migration of the cells. In clinical aspects degradation, biocompatibility, stability, and cost efficiency are the important considerations for the materials utilized for dental tissue engineering.

In dentistry, tissue regeneration includes regeneration of alveolar bone, periodontal ligament, enamel, dentin, and whole tooth. The principle of employing engineering and life science to develop the biological components, to provide a healing/improved efficacy is termed tissue engineering [31]. Bone marrow, fat tissue, and endometrium tissue-based stem cells are also able to differentiate tooth-forming cells (odontoblasts).

Regenerative dentistry employs several techniques, including cell sheets, spheroids, organoids, 3D bioprinting, layered scaffolds, and exosomes [32]. Rapid cell death and poor retention have hampered the effectiveness of stem cell therapy in clinical dentistry. Cells and their extracellular matrix combine to produce high-density sheet structures in cell sheets, a scaffold-free cell treatment [33]. Dense three-dimensional cell aggregates known as spheroids facilitate angiogenesis, inflammation control, and repair. In immunodeficient mice, vascular dental pulp-like tissue has been created using *in vitro*-fabricated prevascularized microtissue spheroids of DPSCs. Organoids is a cell-based regeneration technique that uses adult, embryonic, or induced pluripotent stem cells (iPSCs) to create 3D tissue constructions [34,35]. Since the shortage of DSCs may make their use more difficult, this strategy is beneficial for tooth germ organoids. To evaluate the proliferation and innervation of salivary glands, researchers implanted innervated secretory epithelial organoids produced by a magnetic 3D bioprinting technology into an *ex vivo* animal. The spheroids demonstrated good cell viability and encouraged neuronal and epithelial growth in injured glands, which was a major advancement toward xerostomia brought on by radiation and salivary gland regeneration [36].

Dental pulp regeneration appears to be possible using stem cell-based therapies, although limited cell viability following *in vivo* transplantation presents a problem. Using hypoxia-inducible factor 1α (HIF-1α) stabilization, stem cells from human exfoliated deciduous teeth (SHED) were preconditioned to a hypoxic situation to enhance postimplantation cell survival and pulp tissue regeneration. Following 28 days, there was an increased vascularization and dentin-like tissue development, resembling tooth pulp. The activation of the PI3K/AKT (Phosphatidylinositol 3-kinase/protein kinase B) pathway, upregulated expression of hexokinase 2, hexokinase 1, and glucose transporter 1, and the involvement of Smad7 (mothers against decapentaplegic) in the upregulation of hexokinase 2 and glucose transporter 1 all contributed to the stabilization of HIF-1α, which reduced cell apoptosis and increased survival [37]. Additionally, swine teeth were implanted with dental pulp tissue-derived exosomes and scaffolds loaded with dental pulp tissue-derived exosomes. This enhanced revascularization in immunodeficient mice and encouraged the recruitment and differentiation of SCAPs, ultimately improving dental health [38].

A state-of-the-art manufacturing technique called three-dimensional bioprinting uses standardized ingredients and Computer-aided design digital models to create individualized three-dimensional things. The intricate procedure entails the accurate positioning of cells and biomaterials, enabling spatial control over component placement [39]. Cell-to-cell growth

interconnectivity is another benefit of three-dimensional bioprinting that enhances tissue regeneration. It's anticipated that transplantable organs made via three-dimensional printing will be accessible soon [40]. To create a personalized, load-bearing 3D-printed scaffold for pediatric TMJ (temporomandibular joint) mandibular condyle restoration, Abramowicz *et al.* created a porcine model. Porcine computed tomography was used to 3D print the scaffolds and BMP-2 (bone morphogenic protein 2) was applied to them. The physical characteristics of the reconstructed scaffolds were comparable to those of the unoperated condyles, producing new bone and preserving the proper condylar height. The stiffness of the reconstructed condyle revealed 20 to 45 percent of the control side. According to the study's findings, these scaffolds can promote regeneration without impairing functional results [41].

In dentistry, multilayer scaffolds are particularly useful for promoting periodontal tissue regeneration. Using CAD, this method creates 3D constructs layer by layer with the help of growth factors, biomaterials, and stem cells. This allows for the creation of multiphasic scaffolds, each layer of which is intended to regenerate a particular area of the periodontium. These scaffolds are made by a hierarchical architecture that can direct the concurrent tissue regeneration. This method works well for generating linkages between hard and soft tissues and is appropriate for tissues with complex anatomical structures [42,43]. To promote soft-hard tissue regeneration, Laucsh *et al.* developed a multilayered collagen scaffold with an emphasis on interlayer cohesiveness in 2018. A unique tri-layered intrafibrillar mineralized collagen and HA mimicking the structure of the periodontium, comprising the cementum, ligament, and bone, was created by them using a mineralized system. Within six days, the scaffolds had a 1.76 calcium/phosphorus ratio, indicating significant mineralization. Making a trilayered collagen scaffold for periodontal regeneration is possible with the help of the model system [44]. In another investigation, a trilayer porous scaffold based on chitosan was created to restore the cementum, gingiva, bone, and periodontal ligament all at the same time, thereby promoting periodontal regeneration. Two sections of the scaffolds were made for the regeneration of bone and gingiva, while a third section was made for the regeneration of periodontal ligament. Rapid equilibrium water content was seen during *in vitro* characterization, however high biocompatibility, tissue ingrowth, and vascularization within the scaffold were observed during *in vivo* studies. With a thick mineralized matrix inside the medium molecular weight-chitosan area, a resorbable trilayer scaffold is a viable option for periodontal regeneration [45].

Exosomes released by mesenchymal stem cells provide a therapeutic alternative that is cell-free for immune response control, signal transmission, and epigenetic alteration in regenerative dentistry. Due to their low immunogenicity, high drug loading capacity, biocompatibility, stability, specificity, and lack of cytotoxicity, they may be used to regenerate dental soft tissue and dentine pulp [46]. In 2020, Benton Swanson and colleagues investigated a novel biomimetic pulp capping therapy using controlled release of odontogenic exosomes from a biodegradable carrier for dentinogenesis. The findings of this study demonstrate that an amphiphilic triblock copolymer can effectively enhance tissue neogenesis by encasing and releasing exosomes produced from cells at dental pulp lesions. Exosomes formed from immortalized murine odontoblasts (MDPC23 cell line) and human

dental pulp stem cells were released, leading to migration and differentiation as well as the possible delivery of exosomes derived from cells for medicinal purposes [47]. Biological substances are transferred by the enriched exosomes that make up small extracellular vesicles (sEVs), which help to repair damaged cells and tissues. By changing the inflammatory phenotypes of macrophages to anti-inflammatory ones and restoring their ability to differentiate into osteogenic tissue, they aid in the regeneration of periodontal tissues. Exosomes have better immunomodulatory effects when inflammatory cytokines are present. Using lipopolysaccharide-preconditioned dental follicle cells (L-D-sEV), Yanli Huang studied in 2024 the effects of small extracellular vesicles on periodontal ligament cells from periodontitis-affected teeth (p-PDLCs) *in vitro* and mice. Findings indicated that treatment of L-D-sEV dramatically reduced the levels of phosphorylation of c-Jun N-terminal kinase and p38 protein in p-PDLCs, decreased the rate of apoptosis, down-regulated genes associated with apoptosis, and up-regulated the levels of B-cell lymphoma-2 gene. L-D-sEV treatment *in vivo* slowed osteoclast activity, increased M2 polarization, and decreased alveolar bone loss [48].

4. Biomaterials used in tissue engineering

Biomaterials including both natural/chemical play a vital role in dental tissue engineering. The cellular microenvironment required for optimal dental tissue regeneration was obtained by biomaterial fabrication utilizing frameworks such as scaffolds, matrices or constructs with interconnected pores. Scaffold design depends upon the biomaterials selection, physical/chemical /mechanical properties optimization and advanced fabrication techniques. Whereas tooth regeneration depends upon both scaffold based approach or scaffold independent approach.

Bone, cartilage, tendon, muscle, skin *etc*. are the protenaceous substances observed in the extracellular matrix and is biocompatible/biodegradable collagen extracted from several allogenic sources. The peculiar property of collagen make it widely utilized in dental regenerative research and collagen serve as the predominant structural protein found in the extracellular matrix of several dental tissues. The higher tensile strength material collagen gets degraded by enzyme collagenase under mild inflammatory reaction. Type I collagen elicits the Osteodentin formation. Bone conductivity associated with improved mechanical properties has been observed with hybrid scaffolds. The mechanical and physical properties of collagen may be modified by cross linking (glutaraldehyde/diphenylphosphoryl azide) which may improves the mechanical stiffness. Type I collagen supports the osteodentin formation [49].

For dental tissue regeneration various polymers such as polylactic acid (PLA), polyglycolic acid, polylactide-co-glycolide, calcium phosphate materials and silicates are utilized. In case of cementum generation copolymers are also used. For dental tissue regeneration ceramics materials are widely used. The osteogenic gene expressions are afforded by the bioactive glasses and ceramics [50]. Biocompatible/bioresorbable calcium phosphate resembles tooth. Poly (lactic-co-glycolic acid)/nano bioactive glass

ceramic/cementum protein 1/chitin- poly (lactic-co-glycolic acid)/fibroblast growth factor 2/platelet-rich plasma derived growth factors utilized as nanocomposite scaffold.

Biocompatible, non-reactive, and having good mechanical, osseointegration, corrosion, wear, ductility, and hardness qualities are all necessary for a biomaterial [51]. The location of the implantation and the patient's medical history, as well as the function of the surrounding tissue and organs, may affect the ideal characteristics. In addition to restoring lost or injured tissue, biomaterials, and technology are also encouraging tissue regeneration. When it comes to a biomaterial's distinguishing qualities, colour usually plays an essential part. The way that objects are perceived colour is determined by their luminous reflectance and dominant wavelength (λ), which correspond to perceived colour. This results in the classification of items into achromatic scales. The term "chroma," which sometimes refers to colour saturation, describes how much achromatic colour differs from the colour spectrum [52,53]. Because they influence the structural arrangement and motion of atoms, thermal properties play a critical role in controlling the performance of biomaterials used in dentistry. Temperature variations during cavity preparation and resin composite material curing are monitored using methods such as thermocouples and thermometers [54,55]. Non-metallic materials exhibit heat conductivity that is comparable to that of dentin and enamel. Fluid viscosity is either dilatant, pseudoplastic or Newtonian and is directly proportional to the shear rate. Understanding electrical conductivity and resistivity—whose resistivity varies depending on the type of material is crucial to comprehending the structure of materials [56]. The efficacy of dental biomaterials for tooth restoration is assessed with the use of mechanical characteristics and characterization techniques, which also serve to pinpoint probable reasons for clinical deficits resulting from mechanical failure. In addition to external forces from orthodontics, dental trauma, and tooth movement, force is an applied energy that moves or deforms a material. It can be axial, vertical, horizontal, torsion, or bending. Destructive testing techniques, such as tensile, compressive, fatigue, impact, brittleness, hardness, and wear resistance, are used to determine the mechanical properties of dental materials. Elastic and plastic regions are the two types of stresses that make up the stress-strain graph [57,58]. The term "biocompatibility" describes a material's capacity to carry out its intended purpose without endangering the receiver. The term "toxicity" describes a substance's chemical potential to harm living things, while "biodegradation" turns innocuous substances into harmless by-products. A material's capacity to induce particular biological effects and establish a connection with tissue, mediated by the release of bioactive compounds and ions, is referred to as bioactivity. Osseointegration, which is impacted by material, tissue, and surgical variables, is the direct interaction of an implant surface with bone in the absence of fibrous tissue [59,60]. Materials with osteoinductive properties include poly-hydroxyethyl methacrylate, titanium, HA, biphasic calcium phosphate, carbonated apatite, and octacalcium phosphate. Osteoinduction is the process by which undifferentiated bone cells differentiate into osteoblast cells. Inflammatory cells and an avascular, thick collagen capsule are deposited around implanted items or devices in cases of foreign body responses [61,62]. The different biomaterials reported for dental tissue regeneration are showed in Figure 2. The different classes of natural biomaterials used for tissue regeneration was discussed below.

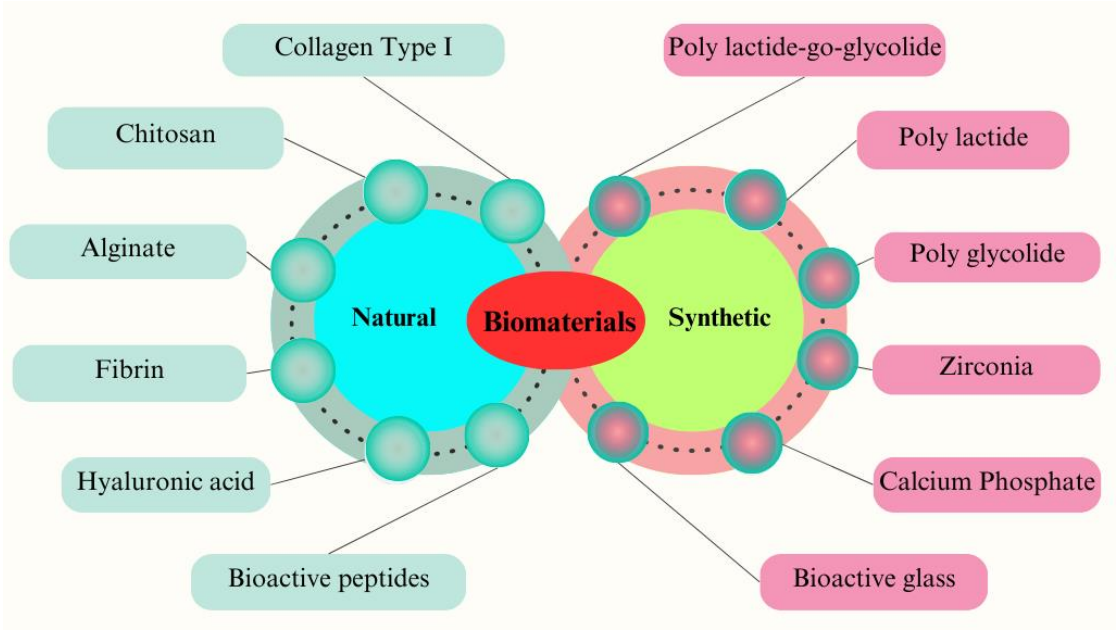

Figure 2. Biomaterials (natural/synthetic) reported for dental tissue regeneration.

4.1 Collagen Type I

The most prevalent kind of collagen in connective tissues, such as blood vessels, skin, and bone, is type I collagen. It is the primary structural protein in these tissues, making up 80% of all proteins and 95% of the collagen in bone [63]. The protein collagen is made up of more than 1400 amino acids twisted into a tight triple helix. The N-terminal non-triple helical domain, the central triple helical domain, and the C-terminal non-triple helical domain are the three primary domains of type I collagen. Several glycine-X-Y repeats facilitate the unique triple-helical domain, resulting in the formation of a microsized fibril with the D-period, a 67 nm banding characteristic. Posttranslational changes to type I collagen molecules provide proper structural conformation as well as mechanical competency [64,65]. Collagen products like Ateloplug, which promote hemostasis and expedited wound healing, have been clinically proven to work. Dressings containing collagen encourage ECM remodeling and lessen postoperative discomfort and edema [66]. More than 30% of vertebrate tissues contain collagen, a biomaterial with several advantages including non-antigenicity, biodegradability, bioresorbability, non-toxicity, and compatibility with synthetic polymers. In addition, it is hemostatic, encouraging blood coagulation, and readily manipulated to provide desirable materials. Collagen is utilized in periodontal and implant operations in dentistry, as well as for bleeding control, wound dressing, graft closure, and healing promotion. Dental pulp tissue uses collagen type I fibers as scaffolding to assist cell attachment, proliferation, and differentiation during tooth regeneration [64]. Additional molecules like chitosan, hyaluronic acid, apatite, bone morphogenetic protein (B]MM-2), and calcium silicate can be added to these scaffolds to improve them [67–69].

The native collagen molecule's conformation is vitally maintained by water, but the structure is unstable when hydrogen attaches to the backbone. The whole triple helix is

covered with a hydration shell that acts as a biological lubricant during collagen self-assembly, setting the interhelix spacing. Collagen molecules would group without the hydration shell, creating kinetically locked amorphous states. Because collagen type I is biocompatible and has a low immunogenicity, it is frequently utilized as a scaffold in tissue engineering. Although it has minimal physical strength, it is enough for the regeneration of tooth pulp. Though it might affect cell survival and biocompatibility, chemical cross-linking can increase the mechanical stiffness of the collagen scaffolds. Connective tissue that has been endodontically treated has been recellularized and revascularized due to the implantation of hybrid scaffolds containing growth factors [70,71].

The bioactive, as well as chemotactic potential of a collagen/gelatin hydrogel with different fibronectin doses, was evaluated by Maria Luisa *et al.* in 2021 on human apical papilla cells. Cell viability, adhesion, and spreading of the hydrogels were compared. Higher concentrations of fibronectin led to increased migration, spreading, adhesion, viability, and gene expression of pulp regeneration markers in human apical papilla cells, whereas the collagen/gelatin 8:2 group had superior outcomes [72]. Another study used periodontal ligament distraction osteogenesis to look at changes in the expression of matrix metalloproteinase-1 and collagen types I and III in beagle dogs. Five groups of twenty dogs each were force-loaded for varying lengths of time. On one side, periodontal distraction osteogenesis was used to induce the first premolar movement, while conventional orthodontics was used on the other. The first premolar on one side (Exp) moved more quickly on the lower arc, and the Exp side's periodontal ligament tissue had greater remodeling. On the Exp side, Coll III and MMP-1 expression peaked at greater levels. Additionally, after 90 days of retention, MMP-1 expression recovered to normal, and this study did not find any significant differences in Collagen I expression between the lower ach of one side and other sides under force loading [73]. Honda *et al.* investigated the implantation of mesenchymal and epithelial cells on collagen scaffolds using the cell-seeding approach in immunocompromised rats. Its potential for regenerative tooth formation was demonstrated by the ensuing tooth morphology, which was similar to that of normal teeth [74].

Chia-Lai *et al.* conducted an *in vivo* study on collagen membrane reactions, revealing two types based on physicochemical properties and processing techniques. Membranes induced by mononuclear cells maintain their structure for 60 days, while collagen-based materials are dominated by mononuclear cells [75]. Recently, a study focused on the development and characterization of resorbable collagen type I membranes (Green Membrane®) for guided bone regeneration. The membrane's surface morphology was analyzed using SEM and 3D systems, and *in vivo*, skin sensitization and toxicity tests were conducted on Wistar rats. The results showed the membrane was homogeneous, non-cytotoxic, and suitable for guided bone regeneration due to its biocompatibility profile [76]. Collagen type 1 is essential for creating reparative dentin, and propolis's advantages make it a desirable ingredient for combining conventional and complementary treatments. The goal of using propolis and calcium hydroxide together as a pulp capping material is to address existing drawbacks. Nirawati Pribadi *et al.* 2021 studied the expression of nuclear factor kappa B and collagen type 1 on dental pulp following a calcium hydroxide and propolis treatment in rats.

Thirty rats were separated into three groups, and their teeth were pulled for the study. Cention which regulates pH and prevents dental caries under acidic conditions, was given to the control group, calcium hydroxide was given to the second group, and a mixture of both was given to the third group. The findings demonstrated that calcium hydroxide and propolis together reduced nuclear factor kappa B expression and increased collagen type I to limit pulp inflammation and promote regeneration [77].

4.2 Chitosan

A naturally occurring, biodegradable, and biocompatible polymer, chitosan promotes tissue regeneration and cell proliferation. Chitosan scaffolds have been modified to improve their osteoconductive and efficiency for applications involving the healing of bone defects. These modifications have included the inclusion of apatite, wollastonite, glass-ceramic, and whitlockite. Because it comes from chitin, a naturally occurring substance that is easily accessible, it is non-toxic, biocompatible, and biodegradable. A chitin derivative derived from the exoskeleton of crabs and shrimp, chitosan is made up of linearly distributed β-(1-4)-linked and N-acetyl d-glucosamine units in straight chains of monosaccharides [78–81].

For chitosan, the NH group is essential to its water solubility, whereas chitin is insoluble in organic acids. Both hydroxyl (-OH), as well as amino (-NH2) groups found in chitosan, may create covalent and hydrogen interactions with other molecules. Chitosan may combine with metal ions to generate complexes that are useful for detoxifying heavy metals and treating wastewater. Additionally, it demonstrates biological activities such as hemostatic, mucoadhesive, antifungal, and antibacterial qualities. The mucoadhesive property is influenced by the degree of deacetylation, with greater degrees improving the mucoadhesive property. Because chitosan is cationic, it interacts electrostatically with negatively charged substances like sialic acid and epithelial surfaces. These interactions may improve chitosan-based formulations' adherence and absorption, which may affect biomedical applications and drug delivery systems. The mucoadhesive characteristic of chitosan is mostly determined by the electrostatic interaction between the negatively charged mucus and the cationic chitosan [82,83].

Chitosan is a multipurpose substance that is employed in root canal treatment, antibacterial tissue regeneration, mechanical integrity, caries prevention, and dentin matrix applications. Additionally, it can be applied to periodontal tissues to give antibiotics, avoiding oral mucositis and fungal infections. Because chitosan satisfies these characteristics, it is also a suitable substrate material for periodontal tissue regeneration. Tissue loss has been significantly reduced by a dentifrice based on chitosan that is sold commercially and does not include fluoride. Enamel regeneration is being investigated using restorative formulations based on chitosan. Chitosan is being used as a carrier for stem cell repair due to recent advancements. Chitosan applications in various dental fields, including surgery, implants, conservative dentistry, wound healing, and prevention [84–86].

Chitosan is a polymer scaffold that promotes regeneration and increases the vitality of human dermal pulp stem cells and exfoliated deciduous dental stem cells. Nevertheless, chitosan is deficient in cell signaling molecules, which are essential for regeneration. For cell

growth and residence, an optimal microenvironment, also known as a stem cell niche, is required. A recent study has developed a chitosan scaffold with cobalt added for human dental pulp stem cells to have the ability to regenerate. In a cell-seeding experiment, the outcomes demonstrated that the Cobalt-incorporated chitosan scaffolds proved non-cytotoxic and improved cellular adherence. The study also discovered that a porous, biocompatible scaffold with improved cellular adhesion for dentin-pulp regeneration was produced by adding 100 μmol/L of cobalt chloride and 2% chitosan solution in a 1:1 ratio [81]. In 2023, Elham Hoveizi *et al*. carried out a study to examine the effects of titanium oxide nanoparticles and human endometrial stem cells on dental pulp regeneration and repair in an *in vivo* animal model. In the study, human endometrial stem cells were positioned on a three-dimensional scaffold made of chitosan and titanium oxide nanoparticles, exposed to pulps, and then covered with the scaffolds. The combined group had more dentine overall and in better quality at 8 weeks than the other group of animals. Dentine formation was accelerated and improved in quality when combined with these three combinations [87]. In 2018, Maxime Ducret *et al*. developed chitosan-enriched fibrin hydrogel to regenerate human tooth pulp. Dental pulp mesenchymal stem/stromal cell survival, antibacterial efficacy, and microstructure were examined in this study for several formulations. 10 mg/mL fibrinogen and 0.5% chitosan at a cytocompatible pH was determined to be the most appropriate formulation. The analytical comparison revealed comparable dental pulp-mesenchymal stem/stromal cell viability and strong antibacterial activities [88].

A study was carried out in 2021 to ascertain the impact of chewing gum based on chitosan on salivary *Streptococcus mutans* counts and the salivary pH. 36 dentistry students participated in this trial and were divided into two groups. One group received chewing gum containing chitosan, while the other group received chewing gum containing a placebo. The two groups' salivary S. mutans colonies differed significantly, according to the data. Nonetheless, the chewing gum containing chitosan caused a statistically significant rise in salivary pH of 0.17. According to the study's findings, chewing gum with chitosan reduces *Streptococcus mutans* colonies [89]. To enhance periodontal regeneration, Qasim *et al.* created porous chitosan membranes employing freeze gelation with or without hydroxyapatite. The shape, physiochemical characteristics, water absorption, breakdown, mechanical attributes, and biocompatibility with osteogenic cells of the membranes were all studied. Membranes displayed 85–77% porosity, according to μCT (micro-computed tomography) studies. The mechanical properties and degradation rate of chitosan and hydroxyapatite composite membranes were found to support cell proliferation and long-term matrix deposition in human osteosarcoma cells and human embryonic stem cell-derived mesenchymal progenitors, suggesting potential use for periodontal regeneration [90]. In 2021, Golnaz Navidi *et al*. developed therapeutic bio-composites to improve the odontogenic and osteogenic development of mesenchymal stem cells generated from human dental pulp *in vitro* regeneration. Chitosan, calcium-silica alumina phosphate (SAPO-34) monometallic, and/or iron-calcium silica-alumina phosphate bimetallic nanoparticles were included in the scaffolds used in this investigation. The scaffolds had a mild impact on cell proliferation and a beneficial effect on differentiation. Osteogenic differentiation was aided by the addition of

ferrous carbonate. According to the study, iron-calcium-silica alumina phosphate/chitosan offers good potential for the engineering of hard tissues [91].

Dental implants are necessary for reconstructing and rehabilitating the mouth. In 2020, Park *et al.* used chitosan and graphene to create a hybrid dental implant. Under ideal circumstances, the GC hybrid implant encourages osteoblast growth while decreasing bacterial activity and biofilm development. The results of this study demonstrate the potential of this hybrid graphene-chitosan implant as a novel kind of dental implant and provide a useful design for the production of cutting-edge dental implants [92]. When Resende *et al.* examined toothpaste formulations including biosurfactants, sodium fluoride, or fungal chitosan against Streptococcus mutans biofilm, they discovered that the results were comparable to those of commercial toothpaste [93]. To remineralize demineralized enamel, phosphorylated chitosan nanocomplexes and amorphous calcium phosphate were used. An enamel crystal-like biomimetic system using amelogenin and chitosan hydrogel revealed that the viscosity of the chitosan had a major impact on the formation of crystals and the imbibition of minerals, producing accretions that were irregularly mineralized [94]. Compared to enamel, dentin mineralization is a distinct process, and it has been discovered that carboxymethyl chitosan strengthens dentin structure [95]. On titanium dental implants, chitosan coating may improve osseointegration and eventually lead to commercial biofunctionalization. Nevertheless, a thorough clinical investigation utilizing sizable samples, established procedures, and extended observation is necessary to validate this hypothesis. It is anticipated that in the future, chitosan coatings for titanium implants will be offered for sale [96].

4.3 Alginate

Alginate, a natural linear polymeric acid group polysaccharide extracted from a brown sea alga, is used as a biocompatible scaffold in hydrogels for drug delivery. A variety of marine algae, including *Laminaria* and related species are also used in the commercial production of alginate [97–99]. Alginate is advantageous for microencapsulation due to its ability to form crosslinking by divalent cations, enabling the fabrication of microgels under mild conditions and providing a proper 3D microenvironment for living cells [100,101]. Alginate facilitate rapid crosslinking by divalent cations. The divalent cations bind to the G-blocks of alginate chains, which is the primary mechanism by which alginate is cross-linked with divalent cations [102,103]. Its porous, hydrophilic structure facilitates oxygen, nutrient, and waste transportation, making it a preferred material for cell and protein delivery [104].

Because alginate-based scaffolds are biocompatible and biodegradable, they may be coupled with other materials or altered with certain ligands, making them attractive for use in dental tissue engineering and regenerative medicine [105]. Ionic cross-linking weakens alginate's mechanical stiffness but can be improved with calcium content (Ca^{2+}) and cross-linking density. Stable covalent crosslinked alginate hydrogels have greater strength and swelling ratio, and arginine-glycine-aspartic acid-modified hydrogels promote cell adhesion [71]. Alginate hydrogel improves periodontal regeneration and dentin pulp and can be used for successful dental

implantation. When used as a root canal filling material, Alginate offers a promising solution for endodontic treatment, providing a uniform morphology, acceptable sealing ability, minimal cytotoxicity, and excellent biocompatibility, making it a valuable treatment option [106].

Hydrocolloid alginate is a substance that is frequently used in dentistry to create gypsum casts for a variety of therapeutic applications, including bleaching trays, orthodontics, temporary crowns and bridges, mouth guards, and removable dental prostheses [107]. In 2018, Silvia Sancilio *et al.* studied the ability of human dental pulp stem cells (DPSCs) implanted onto alginate and nano-hydroxyapatite scaffolds to mineralize and differentiate. The investigation assesses the presence of oxidative stress, extracellular matrix components, viability measures, and gene expression patterns. The findings validate the viability of DPSCs in tissue engineering and maintain natural bone regeneration by demonstrating that they express markers linked to osteogenic differentiation and encourage calcium deposition and biomineralization while grown onto Alg/HAp scaffolds [108]. To create complete dentures, Hyde et al included 85 patients in a Randomized Controlled Trial (RCT) and used silicone or alginate impressions. Compared to alginate impressions, patients preferred dentures created from silicone impressions (67.9%). Although both dentures functioned well, there is strong evidence that patients preferred silicone dentures [109].

For endodontic regeneration, Liang *et al.* developed gelatine methacryloyl-alginate core-shell microcapsules, which demonstrated increased rates of cell proliferation and the formation of pre-vascularized microtissues. Also, improved microvessel formation and pulp-like tissue regeneration were demonstrated in *in vivo* tests [110]. A novel injectable hydrogel microsphere containing human dental pulp stem cells and vascular endothelial growth factor was developed by Zhang R *et al.* Pure alginate exhibited the least degradation, with cell survival rates over 90%. According to a study, self-cross-linkable hydrogels derived from carboxymethyl chitosan and oxidized alginate were utilized for dental enamel regeneration *in vitro*. These hydrogels show antibacterial activity against Streptococcus sobrinus and mutans as well as self-healing characteristics [111]. Human dental pulp stem cells combined with alginate/fish gelatine hydrogels formed the center of the cell blocks made by Lai WY *et al.* The perimeter of the blocks was composed of umbilical vascular endothelial cells infused with silicone ions in fish gelatine methacrylate. The cell blocks had enhanced environment mimicking, elevated expression of angiogenesis-related markers, and increased expression of odontogenic-related markers, rendering them appropriate for endodontic regeneration [112].

4.4 Fibrin

Because of its uniform cell distribution, low immunogenicity, and controlled rate of degradation, fibrin is a gel-based scaffold that promotes tissue regeneration, reduces the diffusion of growth factors, and functions as a binding reservoir and delivery system. It has also been effectively applied to neural and bone tissue engineering to stop additional bleeding [113–115]. Tissue regeneration and wound healing depend on platelet-rich fibrin, a densely packed fibrin complex. It comprises glycoproteins, cytokines, and leukocytes, all of which

are involved in the release of growth factors and the immunological response. Varied endothelial growth factor promotes angiogenesis, whereas cytokines, leukocytes, and lymphocytes block infection as well as inflammatory cascades of inflammation. Ensuring the production of αvβ3 integrin and stimulating angiogenesis, fibrin entraps cytokines such as platelet-derived growth factors, vascular endothelial growth factors, angiopoietin, and fibroblast growth factors. Moreover, it promotes wound colonization, adhesion, and the immune system. Mesenchymal stem cell development is also aided by fibrin. Platelet-rich fibrin also promotes migration, cell adhesion, and osteoblast proliferation, which in turn results in bone formation. It can be administered alone or in conjunction with bone grafts to accelerate bone development and vascularization [116].

Fibrin, by supplying a scaffold with growth factors, augmenting cellular proliferation and differentiation, and stimulating tissue ingrowth, successfully revascularizes juvenile permanent teeth with necrotic pulps. Its slow release promotes increasing thickening of the dentinal wall and stable healing. When traumatic immature teeth with necrotic pulp are treated with calcium hydroxide, dentin support is reduced and root fracture is avoided. It is advised to use platelet-rich fibrin to keep teeth strong and alive while lowering the danger of breakage [117,118]. Fixing agents like poly-llysine help lessen the shrinkage and poor mechanical rigidity that it experiences. Although higher fibrinogen concentrations can improve its mechanical qualities, they also make cell division and survival more difficult. The mechanical characteristics of the hybrid gel scaffold also enhance stem cell migration and differentiation, which is important for regenerative operations [113,119]. It strengthens roots for endodontic regeneration by promoting biomineralization. Results obtained *in vitro* are congruent with those obtained *in vivo*, allowing for more predictable results in regenerative endodontic therapy. A case report details the use of a canal shaper with triple antibiotic paste in the treatment of an avulsed tooth with a periapical abscess. After irrigating the canal, a platelet-rich fibrin was placed, and then biodentine and glass ionomer cement were added. After six months, platelet-rich fibrin assisted in radicular dentin healing and apex closure. According to another investigation, introducing platelet-rich fibrin to gingival recession covered by a coronal advancement flap decreased the levels of Interleukin beta and matrix metalloproteinase 8 at day 10 and then raised them, which helped the periodontal lesion heal [120].

The effects of activated platelet-rich plasma and fibrin glue (FG) on the growth and osteogenic differentiation of human dental pulp stem cells were investigated by Ali Sadeghinia *et al.* Using chitosan-gelatin/nanohydroxyapatite, they made porous composite scaffolds, and they made a-PRP (Platelet-Rich Plasma) by activating whole blood with calcium chloride. In order to seed human dental pulp stem cells, four sets of composite scaffolds were built, and the scaffold surface showed an ordered fibrin network in the 14-day scanning electron microscope picture. Improved human dental pulp stem cell adhesion was seen in all groups treated with Fibrin Glue and activated platelet-rich plasma. The collected cells displayed increased mineralization and osteoblastic development on the composite scaffolds, which had a fibrin network [121]. In 2023, Kao Li *et al.* studied cross-linked hydrogels with and without fibrin for endodontic regeneration as scaffold materials. They developed a

scaffold of gelatin and fibrin and used XRF, dynamic rheology, and cryo-electron microscopy to analyze its structure. The findings demonstrated that whereas gelling together produced a distinct network with double the mineral content and more ductility, gelling gelatin and fibrin separately generated traditional cross-linked networks. The hybrid gel stimulated dentin production, odontogenic differentiation, and increased cell migration [122]. In 2022, Gengtao Qiu *et al.* investigated the growth and osteogenic differentiation of hPDLSCs. According to the study, alginate-fibrin-hPL microbeads released human platelet lysate (hPL) microbeads more quickly than alginate-hPL microbeads. The viability of hPDLSCs was enhanced by the hPL-based medium, and the ideal hPL was 2.5%. This points to a potentially effective xeno-free method for improving orthopedic, craniofacial, and dental regenerations [123].

4.5 Hyaluronic acid

The extracellular matrix of vertebrate tissues is mostly composed of hyaluronic acid (HA), a naturally occurring polymer present in connective tissue that is also biocompatible. Body fluids including serum and synovial fluid are rich in it [124]. HA has a limited potential for immunogenicity, however it degrades quickly *in vivo* and has weak mechanical strength. On the other hand, chemical modification and cross-linking can regulate it. Hyaluronidase breaks down hyaluronic acid enzymatically to produce harmless byproducts [125,126]. Hygroscopic in nature, HA serves as the body's lubricant as well as shock absorber by absorbing and holding onto water molecules. It is non-immunogenic, biodegradable, and biocompatible. It works well in joints and other tissues because of its high viscosity [127,128].

HA is composed of repeated disaccharide units connected by β-1,4-glycosidic linkages. The umbilical cord, epidermis, and synovial fluid have large concentrations of this substance, which is mostly synthesized by the plasma membrane via a class of hyaluronan synthase isoenzymes. In the connective tissue of the gingiva and periodontal ligament, HA synthase enzymes may be identified in various cell types, including osteoblasts, cementoblasts, fibroblasts, osteoblasts, and ligament cells. Its half-life varies from 12 hours to 3 days depending on the cause, which can be either localized metabolism or emptying lymphatics into the circulation. Hyaluronidase, β-N-acetyl-hexosaminidase, and b-d-glucuronidase are among the enzymes that break down HA enzymatically [129–132]. Because of its anti-inflammatory qualities, HA can help arthritic joints feel less painful and swollen. It is helpful in tissue engineering and wound healing because it encourages tissue regeneration and repair. Applying HA topically to soft tissues can improve the osteoblast development and viability of periodontal ligament fibroblasts, boosting the synthesis of new bone and collagen. Owing to its moisturizing properties, it is widely utilized in cosmetics and skin care products. In the field of dentistry, HA shows promise for treating gingival recession, repairing periodontal wounds, and regenerating intra-bony defects [133,134].

Hyaluronic acid gels are injectable and can be used as suitable scaffolds for pulp regeneration due to their ability to regenerate tissue. Injecting HA into soft tissues can enhance the appearance of the smile, gingival recession, and implant success [135]. To improve tooth mobility, HA injections into the periodontal ligament stimulate the expression

of osteoclasts and osteoblasts. Orthodontic therapy-related plaque accumulation and inflammation can lead to gingivitis and periodontitis. Neovascularization is encouraged by the injectable gel treatment's improved papillary regeneration. Injecting HA is a minimally invasive technique that stimulates fibroblast migration and fibrogenesis while addressing gingival and papillary recession in the esthetic zone, with a decent degree of result stability [136]. In 2021, Esteban Astudillo-Ortiz *et al.* developed an injectable, self-setting hydrogel system for endodontic regeneration that is based on hyaluronic acid and enhanced with platelet lysate. The hydrogels demonstrated appropriate microstructure, adherence to dentine walls, and working and setting times. The hydrogels demonstrated characteristics of support and encouraged the migration of cells toward dentin surfaces. In the hydrogel extension, the breaking point was reached with deformations of 1.4056 ± 0.3065 mm and 4.3106 ± 1.8677 mm. These findings point to injectable hydrogels with platelet lysate-loaded HA as a potential biomaterial for endodontic regeneration treatments [137]. In 15 patients with periodontal bone abnormalities, Engstrom *et al.* investigated the anti-inflammatory and bone-regenerating properties of injectable HA. The surgically treated group showed a 2.2% increase in bone height, but the gingival crevicular fluid estimate revealed no immunological response [138].

Mucogingival surgery aims to repair recessions, rebuild lost tissues, restore healthy gingival architecture, and improve the appearance of smiles by correcting gingiva and soft tissue problems. In periodontology, hyaluronic acid has become a prominent therapeutic agent for soft tissue covering treatments because it enhances periodontal attachment renewal, connective tissue thickening, and root coverage [139,140]. According to research, the maxilla (79.35% at 24 months) and mandible (78.71% at 24 months) in the interdental region demonstrated considerable coverage following HA injection into the maxillary and mandibular jaws at 3, 12, and 24 months [141]. A novel treatment option for gingival recession abnormalities appears to be possible as preclinical research showed that HA with CAF (coronally advanced flap) dramatically enhanced periodontal regeneration [142]. The usefulness of applying local HA following surgical extraction of an impacted third molar was investigated by Yilmaz *et al.* Twenty-five healthy adults, ages 18 to 29, with bilaterally impacted lower third molars participated in the study. While the control group did not receive any therapy, the study group's right third molar sockets were filled with 0.8% HA. Assessments were made on edema, trismus, and pain following surgery. The study discovered that following dentoalveolar surgery, HA can have an analgesic effect in post-extraction sockets, minimizing the requirement for nonsteroidal anti-inflammatory drugs [143]. Inuyama *et al.* investigated the effects of HA sponge on severed tooth pulp as well as KN-3 cells *in vivo*. They discovered that HA sponge might be used for dental pulp regeneration because of its stable structure, biocompatibility, and biodegradation. Furthermore, this finding raises the possibility of using HA sponge as a scaffold to regenerate tooth pulp [144].

In 2022, Ibraheem *et al.* showed that using HA therapy improved wound healing in extraction socket wounds [145]. In 2021, Jan Schmidt *et al.* demonstrated that dental pulp stem cell proliferation surface markers, and cell size are all impacted by Low Molecular Weight Hyaluronic Acid (LMW-HA). In patients with chronic periodontitis, Gontiya *et al.* discovered that subgingivally using 0.2% HA gel together with scaling and root planing

reduced gingival index and bleeding index, lowering inflammatory infiltrate [146]. In 2023, the favorable effects of cross-linked hyaluronic acid (cHA) on periodontal wound healing and regeneration were studied by Xilei Zhu *et al.* The results of the study showed that the combination of cHA, HS, and cHA/HS decreased the expression of HA receptors, interleukin-8, biofilm development, and periodontal ligament fibroblasts (PDLF) adherence to the dentine surface. The study also discovered that serum had no detrimental effects on the effectiveness of cHA against PDLF or periodontal biofilm. These results further validate the beneficial effects of cHA on periodontal wound healing cells, indicating a possible role for cHA in non-surgical periodontal treatment [147]. According to Pilloni *et al.*'s study, individuals with periodontitis showed substantial reductions in bleeding on probing as well as better periodontal metrics after receiving HA therapy [148]. Using a 3D-Bioplotter EnvisionTec, Yang *et al.* developed a gelMA methacrylate hyaluronic acid bioink to encapsulate osteocytes. Following 28 days, the cells displayed mature osteocytes, dendritic morphology, and elevated DMP-1 (Dentin matrix protein 1) as well as calcium deposition [149].

4.6 Bioactive Peptides

The bioactive peptide group of substances holds great potential for biofunctional applications because of its low immunogenicity, decreased size, stability, and functional functions. They are essential to physiological and biological processes and are present in all living species. Peptides can function as enzyme process inhibitors and are either free or encoded in proteins. Peptides are little polymers of amino acids that can have lengths between 20 and 100 [150–152]. In the dental specialties of endodontics, coronal restoration, caries control, and dental material modification, they have been thoroughly investigated. It is possible to build peptide-based scaffolds with altered functional, biochemical, or biophysical characteristics. Different encapsulated medications are possible due to their physicochemical properties and customizable mechanical qualities [153]. More than seven thousand native peptides (NPs) have been found to have important physiological roles for humans [152,154]. More than 60 peptides have received FDA (Food and Drug Administration) approval by 2018; more than 600 are presently undergoing preclinical and clinical testing [155,156].

Short polymer chains of amino acids produced chemically, known as synthetic peptides, are employed in tissue engineering and regeneration applications. High chemical and biological variety, potency, selectivity, minimal toxicity, and strong membrane penetration are some of its benefits. Nevertheless, their metabolism frequently exhibits poor stability. Synthetic self-assembly methods have been applied recently to the production of bioactive materials in biological settings. Tissue regeneration is supported by three-dimensional fiber networks formed by self-assembling β-sheet producing peptides. These peptides have a number of uses, including as engineering, wound healing, and tissue regeneration. Additionally, they are biocompatible and effectively target molecular recognition sites [157–160].

Amelogenin is a protein that is employed in the remineralization of enamel and is essential for the formation of enamel crystals. MMP-20 promotes the formation of enamel-like layers, which improves the composition, structure, and mechanical characteristics of artificial

enamel [161,162]. The P11-4 peptide's amino acid sequences generate a 3D hydrogel with a strong affinity for hydroxyapatite, which is why it is used in dental tissue engineering. This peptide has demonstrated promise in stopping early dental caries and rebuilding demineralized tooth tissue. It creates a three-dimensional matrix that aids in the creation of de novo hydroxyapatite and the remineralization of subsurface lesions by imitating enamel matrix proteins [163,164]. The results of a study demonstrate the significance of a favorable milieu for stem cell adhesion and angiogenesis. RAD/PRG/KLT can improve the survival and differentiation of DPSCs, consequently facilitating dental pulp regeneration in partly pulpotomized rat molars [165]. CPD4: VNPKYKQKRR produces biomineralization indicators, increases cell-penetrating activity and osteogenic efficiency in DPSCs, and creates mineralized tissue when combined with collagen gel, indicating possible biotechnological uses [166].

Self-assembled peptide hydrogels are excellent for tooth regeneration and caries therapy because they promote hydroxyapatite nucleation, attach to the adhesive/dentin interface, and are compatible with dental pulp stem cells. Postnatal dental pulp stem cells are aided in growing by dentonin, a bioactive component of the extracellular matrix [159,160,167]. For the development of dental pulp stem cells, Nguyen *et al.* developed a biodegradable self-assembled peptide hydrogel. Nanofibers with β-sheet shapes were formed by the hydrogel, which was composed of dentonin and a peptide framework that self-assembled. Its promise as an optimal bioresponsive matrix for treating dental cavities was validated by its thixotropic properties and cytocompatibility with dental pulp stem cells and fibroblasts [29].

Dental caries is a common condition caused by bacteria in biofilms, and the therapies used today frequently have a negative impact on the variety of oral microbiota and healthy tissues. The efficiency of resin-based composites was increased by the modification of dental materials using peptides. Strong metabolic suppression and localized calcium phosphate remineralization were demonstrated when the antimicrobial peptide AMP2-derivative was incorporated into a monomer site [168]. Yoshinari *et al.* showed that titanium-binding peptides and antimicrobials successfully inhibited the growth of biofilms on titanium surfaces [169]. In 2022, Peng Zhang *et al.* developed pH-sensitive antibacterial pHly-1, which successfully prevents and cures dental caries by taking advantage of the acidic cariogenic biofilm milieu. The study examines the differences in bacterial activity between pHly-1 nanoparticles (NPs) and chlorhexidine, a popular anticarious drug. pHly-1 NPs kill bacteria quicker and more efficiently than chlorhexidine, whose limited antibiofilm capacity restricts its usefulness *in vivo* [170]. Ye *et al.* investigated peptide-mediated dentin remineralization, which appears to be a feasible approach for interfacial integration. The peptide self-adheres to the adhesive/dentin contact, encouraging the repair of damaged dentin matrix [171]. Zhou and colleagues discovered that titanium surfaces became more bifunctional due to the addition of antimicrobial peptides, which improves both their cytocompatibility and bactericidal activity [172]. Similar bone development rates were achieved by *in vivo* dental implants coated with antimicrobial peptide GL13K as compared to conventional non-coated implants [173]. The coating of salivary proteins as well as glycoproteins that covers tooth surfaces is called salivary-acquired pellicle (SAP). A DpSpSEEKC peptide was created by

Yang *et al.* in 2017 to regenerate HAP on demineralized tooth enamel surfaces. As a nucleation template, the negatively charged peptide attaches itself to positively charged areas on acid-etched teeth. As soon as phosphate ions arrive, it collects calcium ions and creates HAP deposits. This peptide has the potential to be a restorative biomaterial for tooth enamel remineralization due to its effective mineral regeneration and enhanced mechanical capabilities [174].

A bioactive treatment for dentin disorders, CPNE7-derived functional peptide (CPNE7-DP) hinders dentinal tubules and regenerates tubular dentin. Although its exact involvement in dental caries is yet unknown, it relieves dentin hypersensitivity and dental caries. Dentin-pulp-like tissue may be formed by implanting CPNE7-DP on fibrin gel and transplanting it into immunocompromised mice [175]. Dentinal hypersensitivity and other non-infectious dentinal abnormalities are successfully treated with CPNE7-DP. Hye *et al.* used a rat model in an experimental investigation on the use of CPNE7-DP in dentin caries. They discovered that CPNE7-DP reduced pulp inflammation and significantly restored tubular tertiary dentin in caries-like conditions. Because CPNE7-DP modulates autophagy, it may have decreased the production of inflammatory cytokines under inflammatory circumstances [176]. The effects of TVH-19, an artificially produced peptide, on odontoblast development and tertiary dentin production in indirect pulp capping (IPC) was investigated by Sili Han *et al.* While TVH-19 greatly aided in cell migration, it did not affect the proliferation of human dental pulp cells. Additionally, it increased the levels of odontogenic gene expression. According to *in vivo* findings, TVH-19 decreased apoptosis and inflammation, promoted the development of tertiary dentin, and downregulated the production of cleaved-Caspase-3 along with interleukin 6. These results indicate that TVH-19 may have uses in indirect pulp capping and show that it can stimulate the regeneration of tooth hard tissue [177].

5. Challenges and opportunities of tissue engineering in dentistry

Tissue engineering field is relatively new, however with a longer history. Understanding of cellular and molecular mechanisms involved in the regeneration of periodontal tissues, differentiation potential of stem cells and stem cells interactions with host tissues are the challenges for tissue engineering in dentistry. The combinatorial research with discoveries in related fields offer newer alternatives dentistry and restorative procedures for clinical application in future. Initially instead of tissue engineering, remineralisation of the demineralised or defective enamel has been focused. The challenging task in dental tissue engineering involves the unique structural and functional nature of dental pulp and non homogeneous nature of dental tissues [178–180]. Hence maintaining physical/mechanical properties for a long time to support newly formed dentinal tissue is the major challenge for scaffold based biomaterials utilized for dental tissue regeneration. Sterilization of pulp space is also a great challenge for researchers focusing towards dental tissue engineering approaches. Growth factors modulation also play major role in stabilization of the dental tissue during dental tissue engineering approaches. Overall the scientific challenges associated with dental tissue engineering approaches include complex nature of oral tissues, lack of ideal scaffold materials, lack of delivery on dental applications, cost effectiveness of

dental tissue engineered products, sterilization protocols, healthcare and related facilities [177]. Whereas, the non-scientific challenges include regulatory issues, ethics, funding opportunities, cost effectiveness, packing, storage and shelf life. The poor understanding on biomimetic approaches and tissues generation creates a point of controversy among researchers, with respect to dentin innervations, histology and chemical structure of enamel, resembling natural enamel, complex nature of enamel due to abundance of minerals and its crystal structure. For instance, enamel (96% HA and hardest tissue) [1] synthesised by amealoblast cells, herein the secretion of enamel tissues similar to natural enamel by amealoblasts is also a great challenge. The major non-scientific challenge as mentioned earlier is the ethical concern for conducting stem cell research (source of stem cells, usage of embryonic stem cells, and handling of cells) [178]. International regulations/guidelines to meet the requirements may offer better solutions globally. Recently it has been reported that biofunctional based materials of polycaprolactone/poly (vinyl alcohol)/chitosan has been utilized for tissue regeneration appliactions in different formulation approaches [181–184].

Progressive delivery of proteins/peptide molecules also creates a great challenging task. The challenges opportunities and commercial products for dental tissue regeneration are shown in Fig 3 and Fig 4 respectively.

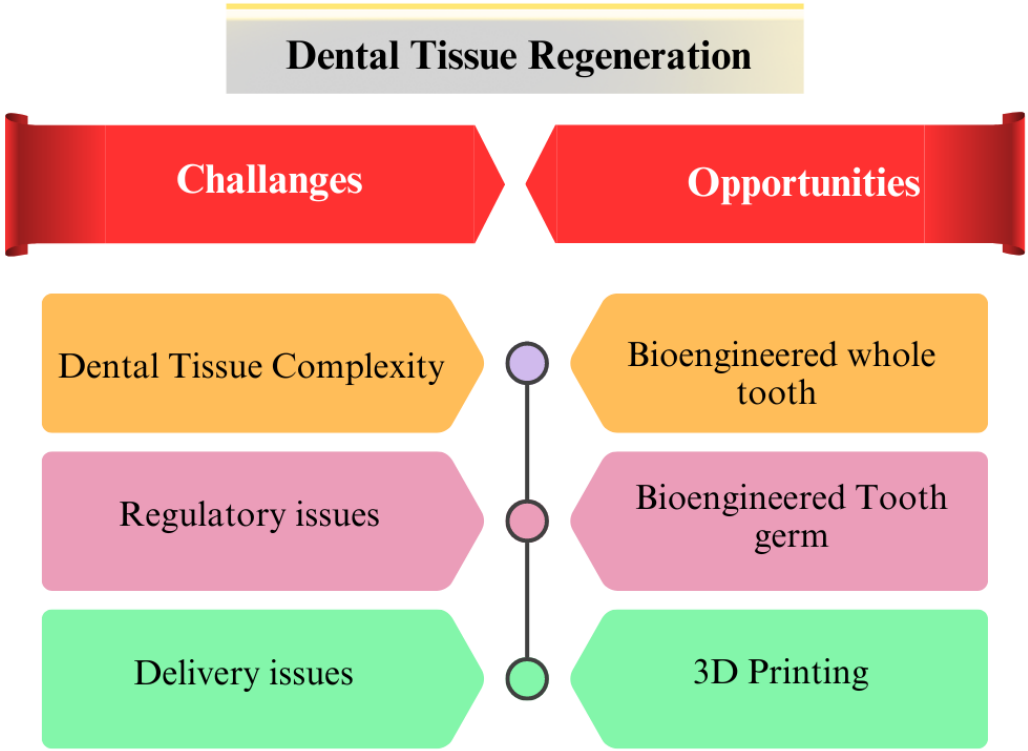

Figure 3. Challenges and opportunities for dental tissue regenerati.

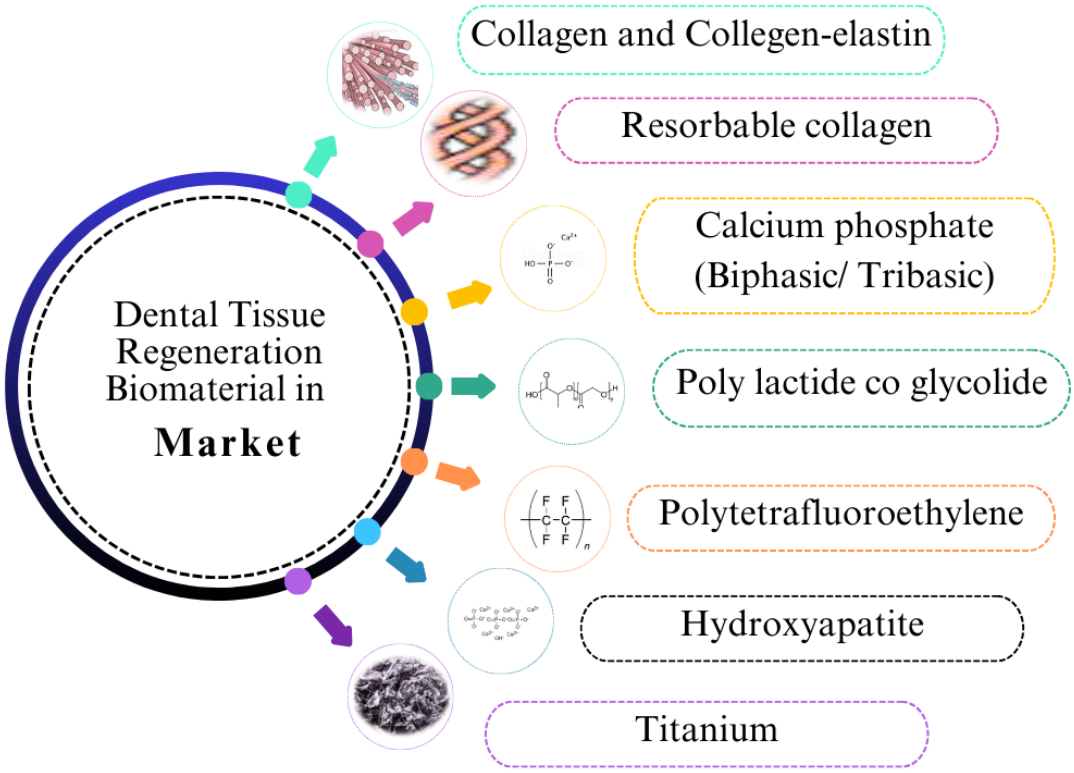

Figure 4. Dental tissue regeneration biomaterials utilized for commercial dental products in market.

6. Concluding Remarks and Outlook

The major dental problems (dental caries, periodontal disease and tooth injury) affects the oral and general health issues. Tissue engineering offers as a new era as therapeutic medicine for those dental problems, and it provides improved cohesiveness and stability to patients undergoing tooth repair. The field of dental materials has seen tremendous growth in the past decades, with a double increase in interest in diverse materials. Bioceramics have been utilized in endodontics, resin composites, dental cement, and bone cement. Examples of these materials are amorphous calcium phosphate and bioactive glass. There has been a rise in demand for restoration materials including dentin adhesives and resin composites. Ceramics research, especially on zirconia, has surged as a result of digital dentistry and CAD/CAM (computer aided design/ computer aided manufacture) technology. In root canal therapy and subgingival dental implants, researchers are also investigating the use of regenerative and bioactive materials [62]. Future approaches to prosthetic dentistry include dentin-pulp complex, whole tooth regeneration, and self-repairing. Research on biomimetic remineralization and tissue engineering is opening doors in these areas. Advanced qualities that mimic natural tissues are present in biomimetic restorative biomaterials, which have been produced through multiple technologies. Nonetheless, difficulties persist because dental tissues are intricate. Notwithstanding these developments, multidisciplinary research is still being conducted to create novel therapeutic approaches, such as biomineralization, which can potentially rebuild the pulp, periodontium, dentin, and enamel. Biomaterials for tissue

engineering, bone regeneration, and dental pulp therapy are being advanced by research in regenerative dentistry, which presents prospects for market expansion. To support vital operations like implants, crowns, and bridges, dental biomaterials are needed more frequently as the aging population becomes more susceptible to dental conditions like decay and gum disease. Opportunities for market expansion are anticipated as a result of the growing need for efficient treatments for age-related dental problems. Cutting-edge methods like 3D printing revolutionize customization by providing exact solutions catered to specific needs and stimulating industry growth and innovation. With a compound annual growth rate (CAGR) of 7.52% from 2024 to 2031, Data Bridge Market Research projects that the global dental biomaterials market will reach USD 17.15 billion by 2031. This prediction is based on factors such as market value, growth rate, segmentation, geographic coverage, and significant players [185,186].

Hence the current advancements in the development of novel regenerative therapy may elicts the emergence of dental products. Newer approaches in science and technology may translate dental tissue engineering approaches in to clinical practices. Much consideration in reproducible oral tissue replacement therapies is highly recommended. Next generation regenerative therapy as a type of bioengineered organ replacement relies on whole tooth replacement acts as an attractive idea. To conclude the better understanding on embryonic development, stem cell biology, and tissue engineering technology may support whole tooth replacement.

Acknowledgment

Funding: All sources of financial support for the project **must** be disclosed in the acknowledgements section. The name of the funding agency and the grant number should be given, for example: This work was funded by the National Foundation of Science with grant number XXX. Author should fill the grant number information during the submission stage. Please make sure the grant number is correctly written.

Conflicts of interests

The authors declare no conflict of interest.

Authors' Contribution

Please make specific attributions of author contribution and responsibility in this part and follow CRediT to define the roles of co-authors. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.".

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