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Review

Biodegradable polymers in dental tissue engineering and regeneration

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Abstract: Over the last decade, biodegradable polymers (BP) replaced traditional non-degradable materials in dental and maxillo-facial surgery, in particular for bone regeneration and periodontal care, due to their ability to break down and be absorbed by the body without producing harmful degradation products, along with their great potential for controlled drug delivery, wound management, dental restorations, and tissue engineering. This review described the physical–chemical characteristics of these materials, classified them based on their sensitivity on hydrolytic or enzyme degradation, and described their recent application in both restorative and regenerative dentistry.

Keywords: biodegradable polymers; biomaterials; tissue engineering; tissue regeneration; endodontic; oral drug delivery

1. Introduction

Oral diseases are a broad class of pathologies, usually with inflammatory progression, that cause the destruction of the supporting apparatus of the teeth and potentially lead to tooth loss [1]. The dental clinical practice aims to control etiologic factors, mainly represented by microbial and bacterial infections, to treat these pathologies. However, these approaches very rarely end with the regeneration of ligaments and bones and recent dental practice uses guided tissue regeneration, bone replacement grafts with exogenous growth factors and tissue-engineered techniques for a complete functional recovery [2]. All these technologies involve the application of materials to support cell proliferation and provide signals [3]. In this contest, biodegradable polymers play an important role,

because they (a) don't elicit an inflammatory response; (b) possess a degradation time coinciding with their function; (c) have appropriate mechanical properties for their intended use; (d) produce non-toxic degradation products that can be readily resorbed or excreted; and (e) include appropriate permeability and processability for designed application (Figure 1) [4]. Typically, biodegradable polymers would be classified in hydrolytically biodegradable polymers (HBP) and enzymatically biodegradable polymers (EBP) based on their bond susceptibility to hydrolytic and/or enzymatical cleavage.

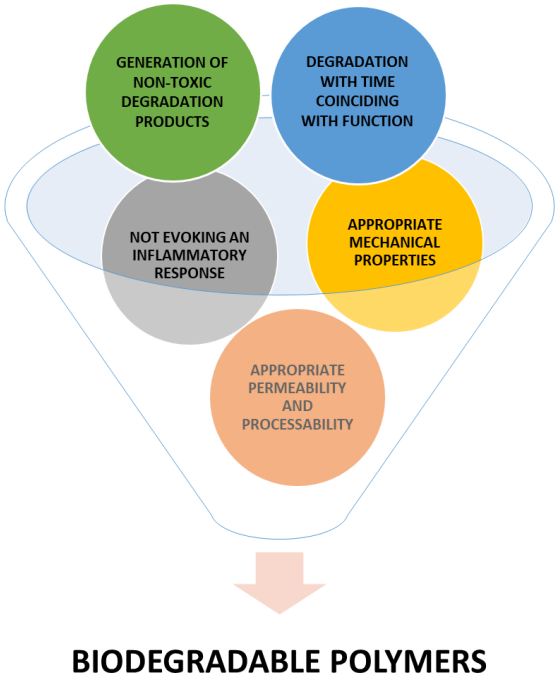


Figure 1. Characteristics of degradable polymers for medical applications.

Based on their physical–chemical characteristics, two classes of biodegradable polymers are available: HBS are characterized by a labile backbone of chemical bonds that deteriorates after water addition and include polyesters (PE) (such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic-co-glycolide) (PLGA) copolymers, polycaprolactone (PCL), and poly(propylene fumarate) (PPF)), polyanhydrides (PAN), polycarbonates (PC), polyurethanes (PUR). EBP present ether or amide bonds on their chain and require catalysis to undergo meaningful degradation under physiological conditions. These materials include synthetically-derived polyethers (PETH), proteins and poly(amino acids) (e.g., collagen, elastin, and fibrin) and polysaccharides (e.g., alginate, chitosan, hyaluronic acid derivatives). In addition, in some materials such as PLA, PLGA, PCL, etc., the polymeric backbones can be subject to hydrolytic degradation due to enzymes or free radicals present in the physiological environment [5,6].

The application of BP in dentistry received major interest for dental regeneration and tissue engineering, although restorative take advantage of polymers controlled degradation rates to release bioactive molecules in a controlled and tunable manner [7]. In particular, anti-bacterial polymeric coatings of Ti oxide chitosan/heparin multilayers have been used by Yuan et al. to prevent biofilm formation and to increase restoration longevity [8]. Travan et al. [9] developed an antimicrobial

nanocomposite using lactose-modified chitosan incorporated with Ag-NPs for the heat polymerized polymethyl methacrylate as prosthetic restaurative material. The *in vitro* results demonstrated that the synthetized nanocomposite effectively killed both gram+ and gram− strains, without any cytotoxic effect respect to osteoblast-like cells, primary human fibroblasts or adipose-derived stem cells. Biodegradable polymers are used in restoration also for the local release of bone stimulating or resorptive drugs in the peri-implant region in order to obtain long-term dental implant success.

BP has also been used in dental regenerative approach as a scaffold for tissue engineering or biomaterials in the form of powders, solutions, or microparticles to stimulate local tissue repair (Figure 2) [10]. In order to enhance osseointegration, Rajeswari et al. [11] developed biomimetic coated titanium surfaces with nano-hydroxyapatite (nHA) and poly(lactic-co-glycolic acid) (PLGA)/collagen nanofibers for dental and bone implant surfaces. The reported data showed that inorganic coating was able to enhance initial cell adhesion, cell proliferation, differentiation and mineralization on the implant surface. Furthermore, Riccitiello et al. [12] proposed electrospun PLA and PCL membranes loaded with resveratrol as promising nanomaterials to preserve post-extraction alveolar ridge volume. The two membranes were able to release resveratrol in a tunable and sustained manner with different kinetic acting simultaneously on two fronts: first counteract bone resorption, the second allows new bone formation.

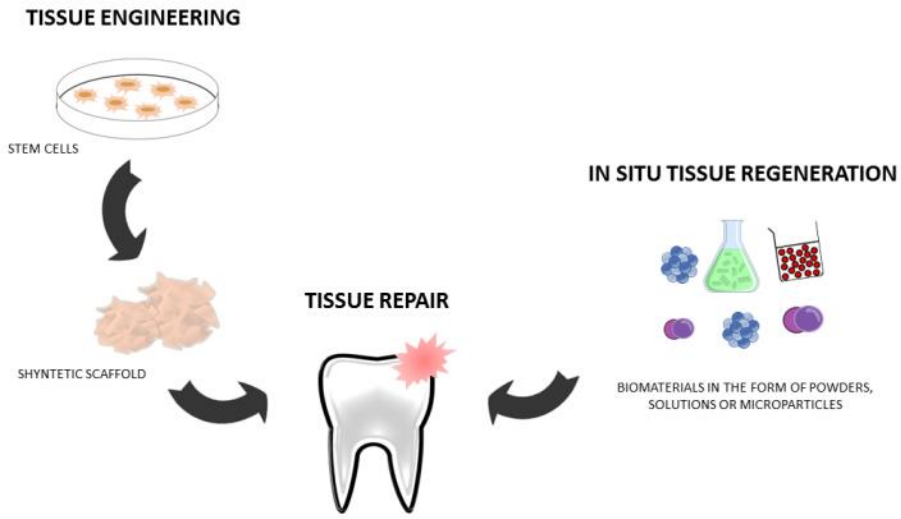


Figure 2. Regenerative route.

2. Hydrolytically degradable polymers

Hydrolytically degradable materials include different polymers such as polyesters (PE), polyanhydrides (PAN), polycarbonates (PC), polyurethanes (PUR).

2.1. Polyesters

Polyesters (PE) are a class of polymers with simple synthesis and facile commercial availability. They have a backbone of aliphatic ester bonds and are mildly hydrophobic. Due to the hydrolytically

stable nature of these linkages, polyesters with short aliphatic chains are utilized as degradable polymers for biomedical applications [13].

Polyglycolide or poly(glycolic acid) (PGA) is one of the first degradable polymers investigated for biomedical use. PGA has melting point (T_m) greater than 200 ℃, glass transition temperature (T_g) of 35–40 ℃ and very high tensile strength (12.5 GPa) [14]. Due to PGA rapid degradation, insolubility in many common solvents and production of glycolic acid as a side product (a substance linked with a strong inflammatory response) [15], limited research was conducted with PGA-based drug delivery devices, while recent papers focus on short-term tissue engineering scaffolds and on its utilization as filler material. Examples are the degradable suture DEXON® [16], the internal bone pin Biofix® [17] and many published works in which PGA is used as a scaffold for bone [18], cartilage [19], tendon [20], vaginal [21], intestinal [22], lymphatic [23] and spinal regeneration [24].

In dentistry, Ohara et al. evaluated the in vivo regeneration of porcine tooth germ-derived cells implanted in polyglycolic acid fiber and β-tricalcium phosphate porous block scaffolds for the formation of tooth bud-like structures [25]. Recently, Chang et al. proposed a chitosan-cPGA (polyelectrolyte complex hydrogel) in order to preserve the height of the alveolar ridge and facilitate bone formation in the alveolar socket after tooth extraction. These results also confirmed in Wistar rats through radiography and histomorphology, showed how injury treated with C-PGA exhibited faster healing than wounds treated with control or no treatment [26].

Polylactide (PLA) is a degradable polyester which possesses chiral molecules and comes in four forms: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), poly(D,L-lactic acid) (PDLLA; a racemic mixture of PLLA and PDLA), and meso-poly(lactic acid). Among these, only PLLA and PDLLA are extensively studied. PLLA has T_g of 60–65 ℃, melting temperature of around 175 ℃ and mechanical strength of 4.8 GPa [27]. The additional methyl group in PLA causes the polymer to be much more hydrophobic and stable against hydrolysis, compared to PGA (high molecular weight PLLA requires more than 5 years to be completely resorbed in vivo) [28]. Then, PLLA is modified or copolymerized with other degradable polymers to reduce degradation time, as shown by the use of radiations to create radicals in the ester alpha carbon which, upon rearrangement, shortens the polymer backbone through the removal of an ester bond and the release of carbon dioxide [29]. PLLA is used as bone fixator, scaffold for bone [30], cartilage [31], tendon [32], neural [33] and vascular [34] regeneration. Similarly, PDLLA is an amorphous polymer with the random positions of its two isomeric monomers within the polymer chain. Poly(D,L-lactic acid) has T_g of 55–60 ℃ and mechanical strength of 1.9 GPa [14]. This polyester requires over a year to properly erode and it is commonly used as drug delivery film [35] and tissue engineering scaffold [36]. All these polyesters, also if classified as hydrolytically degradable, are in vivo effectively degraded by the enzymes lipase, esterase, and alcalase [37].

In dentistry, the maintaining of alveolar ridge dimensions is crucial for a successful placement and functional dental implant. In order to reduce alveolar ridge resorption after tooth extraction, different material can be used in tissue regeneration, such as membranes, graft materials, and biodegradable space fillers [38]. Thomas et al. investigated how the role of PLA space fillers fabricated by fusing porous PLA particles loaded with drugs can help to promote regeneration and maintain the original socket dimensions [39]. Serino et al. proposed Fisiograft, a synthetic copolymer composed of PLA and PGA, as a space filler during ridge preservation. In this study, patients who received Fisiograft after tooth extraction and evaluated 6 months following treatment, exhibited newly formed bone well mineralized and structured, indicating how such bioabsorbable synthetic

material was able to prevent alveolar bone resorption [40]. Riccitiello et al. synthesized PLA- and PCL-loading resveratrol electrospun nanofibers able to induce dental pulp stem cells differentiation into osteoblast-like cells and inhibit osteoclast differentiation [12].

Poly(lactide-co-glycolide) (PLGA) is a polymer derived from the random copolymerization of PLA (both L- and D,L-lactide forms) and PGA. PLGA properties can be modulated through the careful choice of copolymer composition, exhibiting different degradation times due to the simultaneous action of enzymatic and hydrolytic mechanisms [41]. PLGA is the most investigated degradable polymer used in a wide range of medical applications, and an excellent candidate for application in tissue engineering and drug delivery. In fact, PLGA copolymers are used as suture materials [42] and as microspheres, microcapsules, nanospheres or nanofibers to deliver chemotherapeutics [43], proteins [44], vaccines [45], antibiotics [46], analgesics [47], anti-inflammatory [48] and siRNA [49].

Moreover, PLGA demonstrates great cell adhesion and good proliferation properties making it an excellent candidate for application in tissue engineering. In particular, in regenerative dentistry, together with stem cell-based therapy, PLGA scaffolds are used to regenerate damaged tissues.

PLGA is also utilized for alveolar ridge augmentation through the reconstruction of atrophic sites in association with bone allograft and osteoinductive proteins [50] or for bone formation as carrier incorporated with autogenous bone graft [51], morphogenetic protein BMP-2 [52] or simvastatin [53].

In dentistry, PLGA has different applications. For example, PLGA microspheres produced by Sousa et al. are able to deliver amoxicillin at significant levels in the root canal [54] while Chitosan coated PLGA microspheres incorporated with recombinant Streptococcus mutants glucan-binding protein D (rGbpD) are potentially used as a dental vaccine [55]. Similarly, PLGA microspheres with hydroxyapatite and ofloxacin showed good results against *S. aureus* and *E. coli* [56], while PDLLA–PLGA microparticles filled with growth and differentiation factors accelerate osteogenesis, bone maturation, fibers realignment, and cementogenesis of the periodontal apparatus in rats maxillae [57].

Recently, it has been proposed that scaffolds able to overcome the limitations of currently used dental bone grafting materials. Indeed, Brown at al. developed three-dimensional magnesium/PLGA composite scaffolds for dental socket preservation and orthopedic bone regeneration. These scaffolds could decrease inflammation observed with clinically used PLGA devices, increase BMSC proliferation and provide a safe and effective environment for bone regeneration [58].

Shirakata et al. demonstrated how PLGA/hydroxyapatite scaffolds promote cell proliferation, differentiation of stem cells [59] and regenerate bone if seeded with differentiated fat cells [60]. Marei et al. used PLGA scaffolds alone or in combination with mesenchymal stem cells or dental pulp stem cells, against maxillary sinus augmentation, obtaining bone regeneration [61]. Furthermore, PLGA scaffolds with stromal cells from the adipose tissue are able to regenerate bones, periodontal ligaments and cementum layers [62]. Another dental application of PLGA relates to the use of this polymer to create tooth-like structures which are subsequently transplanted *in vivo*. In particular, Zang et al. proposed bilayered poly(lactic-co-glycolic acid) (PLGA)/wool keratin (WK) membranes for guided tissue regeneration (GTR) and as a promising application in periodontal disease. These composites were fabricated using solvent casting and electrospinning methods. Experiments conducted in beagle dogs for different weeks and GTR results showed that these composites could effectively promote the periodontal tissue regeneration after 12 weeks [63]. PLGA is also used for sustained drug release in endodontics. For example, PLGA microspheres produced by Sousa et al.

are able to deliver amoxicillin at significant levels in the root canal [54]. These last examples show the importance of the addition of inorganic components, such as hydroxyapatite or bioactive glass to improve material characteristics. In addition, PLGA microspheres containing simvastatin [64], endothelial growth factors [65] or dexamethasone [66] significantly enhance bone formation. Other applications of PLGA relates to better osteointegration of titanium implants through PLGA microparticles loaded with growth factors [67]. In particular, PLGA microparticles loaded with insulin improved biomechanical retention of titanium implants on type I diabetic rats [68]. Finally, polylactide-co-glycolide surfaces can be functionalized for imparting antibacterial properties [69]. For example, such devices are functionalized by Gentile et al., using nanoscale coatings with layer-by-layer assembly [69].

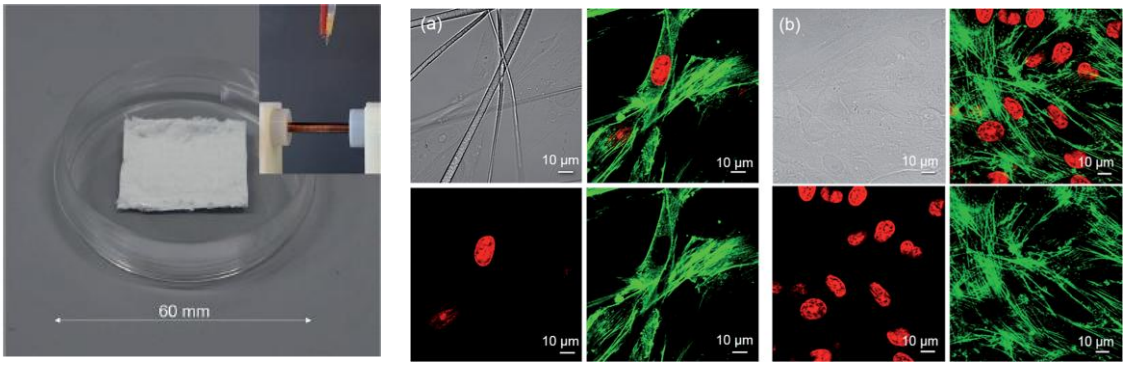
Polycaprolactone (PCL) is a semicrystalline polyester with low *in vivo* degradation rate (due to the synergic action of hydrolytic and enzymatic mechanisms [70]), melting temperature of 55–60 ℃, glass transition temperature of −54 ℃ and high solubility in a wide range of organic solvents [71]. Moreover, it has the low tensile strength (~23 MPa), but very high elongation at breakage (4700%) making it a good elastic biomaterial [15,72]. PCL is used in the production of implants composed of adhered nano/microspheres [73], electrospun fibers [12,74] or porous networks [75] used for regeneration of bone [76], ligament [77], cartilage [78], nerve [79] and vascular tissues [80]. In addition, PCL is often blended or copolymerized with other polymers like polyesters and polyethers to expedite overall polymer erosion [81].

The type of biomaterials used and the manufacturing methods play a fundamental role in the outcomes, contributing to the creation of a favorable environment for cellular colonization, proliferation, and differentiation. In dentistry, PCL elicits odontogenic differentiation of human dental pulp cells (DPSCs). Recently, Louvrier et al. isolated DPSCs from both carious and healthy mature teeth. These cells were able to colonize and proliferate within a polycaprolactone cone and to differentiate into functional odontoblast-like cells secreting ECM similar to mineralized dentine matrix [82].

Similarly, Chuenjitkuntaworn et al. fabricated a 3D-polycaprolactone/hydroxyapatite scaffold and studied its ability to support cell growth, gene expression, and osteogenic differentiation of bone marrow-derived mesenchymal stem cells, dental pulp stem cells, and adipose-derived mesenchymal stem cells. The scaffold supported the growth of all these three types of stem cells and improved calcium deposition [83]. Finally, Baranowska-Korczyc et al. evaluated the antibacterial activity of polymer electrospun materials in three-dimensional (3D) scaffolds for potential dental applications. Polycaprolactone (PCL) was used as a base for gingival fibroblast (HGF-1 cell line) growth and ampicillin was incorporated within the nanofibers and subsequently tested by zone inhibition against an oral strain of *Streptococcus sanguinis*. Such material, able to reduce dental caries pathogen, resulted in a promising material for dental engineering (Figure 3) [84].

Poly(propylene fumarate) (PPF) is a high-strength polyester with the ability to be cross-linked through the unsaturated bonds in its backbone. Then, its degradation depends on molecular weight, cross-linker and cross-linking density [85]. Physically, PPF is an injectable liquid which becomes solid after cross-linking. Poly(propylene fumarate) is used as filling for bone defects [86] and as a depot for the long-term delivery of ocular drugs [87]. Besides, in osteogenic tissue engineering, PPF is used in association with hydroxyapatite [88] or alumoxane [89] to create bioactive scaffolds. Recently, the benefits of such material were combined with osteoconductive HA nanoparticles in order to provide robust, compressive and mechanical properties for bone tissue engineering [90].

In dentistry, Alge et al. produced Poly(Propylene Fumarate) reinforced dicalcium phosphate dihydrate cement composites and implanted them into calvarial defects in rabbits for 6 weeks with mesenchymal stem cells. This material resulted in numerous bone nodules with active osteoblasts within the scaffold pores [91]. Similarly, Shahabi et al developed degradable poly(propylene fumarate)/bioactive glass (PPF/BG) composite scaffolds based on a microsphere technique and investigated the effects of BG content on the characteristics of these composite scaffolds. The silicon released from the BG enhanced the formation of the calcium phosphate layer of teeth [92].



(A) (B)

Figure 3. Electrospun poly(3-caprolactone) scaffold (PCL): a mat composed of PCL nanofibers (A), confocal images of HGF-1 on PCL nanofibers (B), the control sample (a) and after cytoskeleton (green) and nuclei (red) staining (b). Reprinted (adapted) with permission from Ref. [84].

2.2. Polyanhydrides

Polyanhydrides (PAN) is a class of surface eroding polymers that contain two carbonyl groups linked by an ether bond. The degradation of the anhydride bond is highly dependent on polymer backbone chemistry, ranging by over six orders of magnitude. PAN are used for the delivery of chemotherapeutics [93], antibiotics [94], vaccines [95] and proteins [96]. In particular, simple aliphatic homo-polyanhydrides have limited applications due to their rapid degradation, while methacrylated polyanhydrides and cross-linked polyanydrides are used in tissue engineering [97].

In dentistry, these polymers have gained much attention due to their application for oral pathologies. Hasturk et al. studied the effects of the use of calcium hydroxide graft material in combination with polyanhydride around dental implants and extraction sockets, showing how this device provides a great bone-to-implant contact with a well-organized implant-bone interface and a crestal augmentation during immediate implant placement [98]. Uhrich patented a biodegradable polyanhydrides linked with low molecular weight drugs containing a carboxylic acid, amine, thiol, alcohol or phenol group within their structure as polymeric drug delivery systems for oral pathologies [99].

2.3. Polycarbonates

Polycarbonates (PC) are linear polymers with two geminal ether bonds and a carbonyl linkage. Structurally, such connections are hydrolytically stable but PCA possesses rapid surface *in vivo* degradation [100]. The most extensively studied polycarbonate is poly(trimethylene carbonate) (PTMC), fabricated into microparticles [101], discs [102] and gels [103] alone or with polyesters or polyethers [104] for the delivery of angiogenic agents [105] and antibiotics [102]. Moreover, polycarbonates with cyclohexane or propylene in the monomer backbone [106] or with bulky side groups linked through an ester bond to the carbons of the backbone [107] are used in tissue engineering.

In dentistry, polycarbonates are widely used in different applications. For example, Pronych et al. [108] compared the dimensional stability and dehydration of a thermoplastic polycarbonate denture base resin with two conventional polymethyl methacrylate materials. The thermoplastic resins have similar behavior but less dimensional change caused by dehydration. Conversely, Tanimoto et al. [109] proposed an alternative to current metallic orthodontic wires, developing glass-fiber-reinforced plastic (GFRP) wires made from polycarbonate and E-glass fiber. Biological assays on human gingival fibroblasts (HGFs) showed that GFRP wires were not cytotoxic. Recently, Zhang et al. [110] presented a new model for alveolar jaw bone regeneration. They promoted tyrosine-derived polycarbonate polymer scaffolds containing beta-tricalcium phosphate (β-TCP), able to support the rapid regeneration of osteo-dentin-like mineralized jaw tissue using human dental pulp cells (hDPCs).

2.4. Polyurethanes

Polyurethanes (PUR) are biocompatible, moldable, strong polymers that possess ester bonds with geminal amide bonds. Such materials are typically synthesized by polycondensation of diisocyanates with alcohols and amines. PUR consist of both hard and soft segments. The hard segments are composed of functional groups (e.g., amide, urea, or ester-amide) able to form hydrogen bonds, making the structure rigid and unable to undergo conformational changes. The soft segments are of polymenthide chains. The repeating monomers are flexible and withstand conformational changes [111]. For these characteristics, PUR mime body tissues and are extensively used in prostheses like cardiac assist devices [112], small vascular shunts [113] and tracheal tubes [114]. Same properties are available in polyurethane reinforced carbon fibers [115]. In the field of dentistry, PUR is tested as arch models able to regulate the position of the teeth [116] and as substitutes of braces for removable dental aligner restorative treatments (e.g., Invisalign) [117]. Moreover, Lee and Cho created an altered polyurethane casts for a partial removable dental prosthesis that facilitate separation after processing [118] while Selten et al. produced a modified polyurethane foam as a local hemostatic agent after dental extractions [119].

Table 1 recaps the characteristics of the presented hydrolytically degradable polymers.

Table 1. Hydrolytically degradable polymers.

Materials	Classification	Dental application (Refs.)
Polyesters (PE)	(Polyglycolide or poly-glycolic acid) (PGA)	Tooth bud-like structures [25]; Fleece scaffold to counteract the postoperative apical growth of epithelium on teeth [26]
	Polylactide (PLA)	Ridge and socket preservation [39]; Space fillers to promote regeneration and maintenance of original socket dimensions [40]; Prevention of alveolar bone resorption [38]
	Poly(lactide-co-glycolide) (PLGA)	PLGA/hydroxyapatite scaffolds [59,60]; Scaffolds with mesenchymal stem cells or dental pulp stem cells against maxillary sinus augmentation [61]; Scaffold with stromal cells to regenerate bones, periodontal ligaments and cementum layers [62]; Poly(lactic-co-glycolic acid) (PLGA)/wool keratin (WK) membranes for guided tissue regeneration (GTR) [63]; Microspheres delivering amoxicillin [54]; Microspheres with hydroxyapatite and ofloxacin against *E. coli* [56]; PDLLA–PLGA microparticles with different applications in periodontal apparatus in rats maxillae [57]; Microspheres containing simvastatin [64], endothelial growth factors [65] and dexamethasone [66]; Microparticles loaded growth factors [67] and insulin [68] to improve titanium implant
	Polycaprolactone (PCL)	Scaffold for DPSCs differentiation [82]; 3D-polycaprolactone/hydroxyapatite scaffold for different mesenchymal stem cells [83]; Electrospun materials in three-dimensional (3D) scaffolds to reduce dental caries pathogen [84]
	Poly(propylene fumarate) (PPF)	Reinforced dicalcium phosphate dihydrate cement composites [91]; Bioactive glass composite scaffolds [92]
Polyanhydrides (PAN)		The device around dental implants and for extraction sockets [98]; Polymeric drug delivery systems for oral pathologies [99]
Polycarbonates (PC)		Thermoplastic polycarbonate denture base resin [108]; Glass-fiber-reinforced plastic (GFRP) wires of polycarbonate and E-glass fiber [109]; Tyrosine-derived polycarbonate polymer scaffolds of beta-tricalcium phosphate (β-TCP) to support alveolar jaw bone repair and regeneration [110]
Polyurethanes (PUR)		Device for arch models [116]; Substitutes of braces for removable dental aligner restorative treatments [117]; Partial removable dental prosthesis [118]; Local hemostatic agent after dental extractions [119]

3. Enzymatically degradable polymers

Enzymatically degradable polymers are materials that possess bonds that require catalysis to undergo meaningful degradation under physiological conditions. Most of these polymers contain

ether or amide bonds. They are classified in synthetic polyethers, proteins, and poly(amino acids) and polysaccharides (Table 2).

3.1. Synthetic polyethers

Synthetically-derived polyethers (PETH) are highly biocompatible polymers widely used in drug delivery and tissue engineering. PETH are degraded by esterases, also if human equivalents of these enzymes have yet to be identified [120]. All biomedical research with PETH focus on the use of poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG), often in the form of Pluronic ($[PEG]_n$-$[PPG]_m$-$[PEG]_n$) [121]. Pluronic is formulated into hydrogels with relatively weak mechanical properties (maximum shear storage modulus of 13.7 kPa at 20 wt% Pluronic) used for drug delivery [122] and soft tissue engineering [123]. PEG alone is commonly used to cap (PEGylation) or coat other degradable polymers in order to convey steric stabilization, limiting the interactions between the device and the host. This is especially important in preventing phagocytosis of particle-based delivery vehicles [124].

In dentistry, the development of Polyethylene glycol-like coatings (PEG-like) on the titanium surface by plasma polymerization lead to a surface with low bacterial adhesion toward and adequate cell response [125]. PEG was also used by Dabbagh et al. to coat maghemite nanoparticles for treating dental hypersensitivity. These nanoparticles exhibited a significant potential for reducing the permeability of dental tubules but also to transfer other therapeutic agents inside the tubules [126]. Mei et al. [127] developed hydroxyapatite disks with polydopamine-induced-polyethylene glycol coating, finding anti-biofouling effect against a multi-species cariogenic biofilm on the root dentine surface. Thoma et al. used polyethylene glycol hydrogel as a matrix in combination with hydroxyapatite/tricalcium phosphate for guided bone regeneration procedures. The presence of PEG led to a greater bone augmented area [128]. Poly(propylene glycol) is used in dental composites due to its cytocompatibility. For example, Walters et al. affirmed that the use of composites containing PPG results in materials with excellent conversion, depth of cure and mechanical properties, without increasing shrinkage. Moreover, they are more cytocompatible than those containing acrylates [129]. Münchow et al. synthesized an acidic monomer based on polypropylene glycol phosphate methacrylate to constitute a self-etch adhesive system for the enamel [130]. Diniz et al. used thermoreversible Pluronic F-127 hydrogels as a scaffold for encapsulation of dental-derived mesenchymal stem cells in order to test their osteogenic and adipogenic differentiation capacity. After 2 weeks of differentiation *in vitro*, dental pulp stem cells exhibited high levels of mRNA expression for osteogenic and adipogenic gene markers [131]. Pluronic is also used as a drug delivery platform for the prevention and treatment of pathogenic plaque biofilms. Indeed, Mogen et al. demonstrated that Pluronic micelles interact with the biofilm presumably via interaction with the sucrose-dependent biofilm matrix, and are a viable treatment option for plaque biofilms [132].

3.2. Proteins and poly(amino acids)

Proteins are high molecular weight polymers composed of amino acid monomers linked by amide bonds. Proteins and amino acid-derived polymers are used in sutures, scaffolds, and drug delivery devices with prolonged degradation time.

Collagen is the most abundant protein in the human body and is a major component of ligament, cartilage, tendon, skin, and bone. It also forms the structural network of other tissues like blood vessels. Collagen is composed of polypeptide strands bearing triamino acid blocks of Glycine-X-Y, where X and Y are a number of different amino acids, mainly proline and hydroxyproline [133]. These polypeptides are formed into left-handed triple helix microfibrils that organize in different architectures to create collagen fibers with appropriate mechanical properties for their function. Collagen has various medical applications due to its biocompatibility, processability, mechanical strength, and enzymatic degradability by collagenases and metalloproteinases [134]. In fact, it is used as suture material in surgery [135], as depot delivery device in the local extended release of antibiotics [136], DNA [137], siRNA [138], proteins [139] and as hemostatic sealant [140]. In order to improve collagen's potential as a biomaterial, it is combined with other degradable polymers [141] or modified through crosslinking [142], association with bioactive molecules [143] and enzymatic pre-treatment [144].

In dentistry, collagen has been widely tested in regenerative studies. Kim et al. proposed collagen scaffolds loaded with different growth factors such as fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and/or platelet-derived growth factor (PDGF). The implantation of these scaffolds into native root canal tooth revealed re-cellularized and revascularized dental pulp tissue [145]. Collagen-based membranes are also used in periodontal and implant therapy as barriers to prevent epithelial migration and allow cells with the regenerative capacity to repopulate the defect area creating a favorable environment for cellular development. Specifically, collagen bioresorbable membranes for guided tissue regeneration are chemotactic for periodontal ligament fibroblasts, acts as a barrier for migrating epithelial cells, provides hemostasis and serves as a fibrillar scaffold for early vascular and tissue ingrowth [146]. Recently, collagen/fibrin microbeads delivering silver doped bioactive glass (Ag-BG) and Dental Pulp Stem Cells (DPSCs) have shown antibacterial properties against *Escherichia coli*, *Streptococcus mutans* and *Enterococcus faecalis*, revealing a successful approach for applications in tissue regeneration [147].

Elastin is a highly elastic polymer, responsible for contraction of vascular and lung tissues, composed of cross-linked tropoelastin molecules. These molecules are produced intracellularly by smooth muscle cells and fibroblasts and are cross-linked outside the cells to become elastic [148]. Natural elastin is insoluble and elicits an immune response [149]. In order to overcome these limitations, tropoelastin is treated to undergo an irreversible temperature transition above 25 ℃ to change its molecular organization from a disordered to an ordered state, obtaining favorable properties as injectable drug delivery system [150]. Moreover, synthetic elastins are produced through controlled molding, conservation and cross-link [151].

In dentistry, elastin and elastin-like polypeptides are used in association with collagen. For example, Gurumurthy et al. improved the mechanical characteristics of collagen through the use of elastin-like polypeptides. The obtained scaffold allowed osteogenic differentiation of human adipose-derived stem cells cultures [152]. The proliferation and expression of differential markers in osteoblastic cells were evaluated also by Amruthwar et al. to validate the use of these devices for the treatment of alveolar bone loss [153].

Fibrin is a large cross-linked biopolymer composed of fibronectin, involved in the natural clotting process. The use of fibrin as a biomaterial results from its biocompatibility, biodegradability, injectability, and ability to enhance cell proliferation [154]. In dentistry, the most recognized

application of fibrin is in the platelet-rich fibrin (PRF) [155,156], a biomaterial that serves as a vehicle in tissue regeneration, promotes a sustained release of growth factors and stimulates the environment for wound healing [157]. Moreover, PRF is able to stimulate the proliferation of human dental pulp cells, osteoblasts, oral bone MSCs, gingival fibroblasts, periodontal ligament stem cells (PDLSCs) and it augments angiogenesis and regulates the inflammatory reaction acting as a potential scaffold in pulp revascularization procedures of the necrotic immature permanent tooth [158]. In fact, Zhao et al. created a dental scaffold material for tissue regeneration in the oral cavity consisting on cell sheet fragments of periodontal ligament stem cells (PDLSCs) and platelet-rich fibrin (PRF) granules able to promote periodontal wound healing and PDL regeneration in avulsed tooth reimplantation [159]. The second generation of PRF was produced by Dohan et al. introducing a method that concentrated most platelets and leukocytes from a blood harvest into a single autologous fibrin biomaterial [160].

Natural poly(amino acids) are biodegradable, ionic polymers composed of repeated units of one type of amino acid, bonded by amide linkages. The two most commonly studied natural poly(amino acids) used as biomaterials are poly(γ-glutamic acid) (γPGA) and poly(L-lysine), investigated as delivery systems for antibiotics, vaccines, DNA and proteins [161], with intrinsic antimicrobial [162] and antitumor activities [163] and as tissue engineering scaffolds.

In dentistry, Kim et al. produced polymeric calcium phosphate cements incorporated with poly-γ-glutamic acid, in order to confer mechanical strength and to retard hydroxyapatite formation [164]. Poly(L-lysine) is also widely used for the formation of coatings on dental materials. In particular, Varoni et al. studied in vitro and in vivo effects of poly-L-lysine coating on titanium osseointegration. Such coating safely enhanced calcium deposition and implant early osseointegration in animals, suggesting promising evidence to optimize the surface properties of these dental implants [165]. Poly(L-lysine) also exhibits antimicrobial properties as reported by Walters et al. who investigated its antimicrobial properties in mono/tricalcium phosphates–hydroxyapatite composites showing how these composites had great potential in the prevention of recurrent caries and restoration failures [166].

Synthetic poly(amino acids) derive from the industrial polymerization of several homo- and co-poly(amino acids). Poly(L-glutamic acid) (L-PGA) and poly(aspartic acid) (PAA) are considered promising biomaterials in this field. Poly(L-glutamic acid) has the same primary structure of γPGA but with the amide linkage made with the α-carbon amine group instead of the γ-carbon amine group. It is biocompatible, nonimmunogenic and is used as a DNA delivery device [167] and for the construction of layer-by-layer film assembly with negatively charged polymers [168]. PAA is a highly water-soluble ionic polymer with carboxylate content greater than PGA or L-PGA. It is degraded by lysosomal enzymes and it is often copolymerized with other polymers (e.g., PLA, PCL, PEG, etc.) [169] to create micellar structures acting as smart delivery vehicles.

In dentistry, Benkirane-Jessel et al. patented a poly(L-glutamic acid) based compound linked to Melanocortin peptides for the use in endodontic regeneration and for the treatment of dental inflammatory diseases. Such device promotes human pulp fibroblast adhesion, cell proliferation and reduces the inflammatory state of lipopolysaccharide stimulated pulp fibroblasts observed in gram-negative bacterial infections [170]. Osorio et al. developed a novel zinc-doped Portland-based resinous sealing cement linked with poly(aspartic acid) with improved bonding efficacy and dentine remineralization ability. The poly(aspartic acid) application onto demineralized dentine inhibited

mineral phase crystallization, enhancing the remineralization potential of the Portland microfillers at the resin-dentine bonded interface [171].

3.3. Polysaccharides

Polysaccharides are polymers composed of monosaccharide units linked through glycosidic linkages, a type of ether bond. Due to their biodegradability, processability and bioactivity they result very promising biomaterials.

Hyaluronic acid (HA) is a linear anionic polysaccharide, member of the glycosaminoglycan family, consisting of alternating units of N-acetyl-D-glucosamine and glucuronic acid. HA is isolated from rooster combs and bovine vitreous humor, while in humans is found in synovial fluid and vitreous humor and plays where it plays an important structural role in articular cartilage and skin. HA homopolymer is too weak and fluid to create a supportive scaffold, so, in order to overcome this limitation, HA is cross-linked with ethyl esters, benzyl esters or other biodegradable polymers to enhance the mechanical properties while retaining excellent biocompatibility [172]. HA hydrogels are extremely versatile and can be fabricated into sheets, membranes, sponges, tubes, fibers and scaffolds for wound healing [173], regeneration of the trachea [174], cartilage [175], vasculature [176] and nerve tissues [177]. In the field of dentistry, hyaluronic acid shows anti-inflammatory and anti-bacterial effects in the treatment of periodontitis and in endodontic procedures. El-Sayed et al. investigated the effect of local application of 0.8% Hyaluronan gel in conjunction with periodontal surgery. Statistically significant differences were noted for clinical attachment level and gingival recession [178]. Similarly, Gontiya et al. analyzed the clinical and histological outcomes of the local subgingival application of 0.2% HA gel as an adjunct to scaling and root planning in chronic periodontitis patients. The treated sites showed reduced inflammatory infiltrates [179]. As promising scaffold for Regenerative Endodontic Procedures (REPs), Chrepa et al. [180] investigated the effect of Restylane, a Food and Drug Administration approved hyaluronic acid-based gel, on stem cells of the apical papilla (SCAP) in order to evaluate the ability of this gel to induce cell viability and mineralizing differentiation. After a defined time, Restylane promoted greater alkaline phosphatase activity and upregulation of all mineralized markers such as dentin sialophosphoprotein, dentin matrix acidic phosphoprotein-1, and matrix extracellular phosphoglycoprotein. In addition, regenerative potential of hyaluronan scaffolds proposed by Ferroni et al. confirmed the osteo-regenerative properties of these constructs, after implantation into rat calvarial critical-size defects [181]. Finally, similar results were found by Tan et al. who proposed an injectable tissue engineering composite of hyaluronic acid gel (HAG), tooth bud-derived dental mesenchymal cells (DMCs) and transforming growth factor-b1 (TGF-b1). Moreover, its application was further demonstrated in *in vivo* model, in empty tooth slices and pulp chambers of mini pigs. This injectable scaffold would give a great contribution to the future clinical regeneration of dentin-pulp in REPs (Figure 4) [182].

Chitosan (CS) is the deacetylated derivative of chitin, a linear polysaccharide consisting of β-1,4 linked N-acetylglucosamine units that form the exoskeletons of many arthropods. This polysaccharide is composed of randomly located units of D-glucosamine and N-acetylglucosamine and is degraded by the enzyme chitinase, chitosanase, lysozyme, cellulase, protease, lipase and pepsin [183]. Chitosan degradation rate depends on the degree of acetylation and crystallinity and can be regulated through the modification of side groups [184]. Moreover, CS is water absorptive,

oxygen permeable, haemostatic, chemoattractive, antibacterial and assists wound healing [185,186]. However, chitosan is mechanically weak and it is often crosslinked or combined with other degradable polymers to form films, membranes, sponges, particles, fibers, and gels used for bandages [187], delivery devices [188,189] and tissue engineering scaffolds for regenerative applications [190]. Uses of CS in dentistry are related to its antibacterial and wound healing actions. Busscher et al. evaluated the effects of a chitosan on bacterial adhesion and growth on chitosan treated pellicles founding a reduction in bacterial adhesion and bacterial death upon contact [191]. Chitosan has been used in the development of drug control releasing systems in order to overcome endodontic failure, affected by microbial infections in the root canal system and/or the periradicular area. In particular, Barreras et al. combined the properties of chitosan nanoparticles as drug carriers to enhance the antibacterial effect of chlorhexidine showing promising results to improve regenerative procedures in periapical surgery [192].

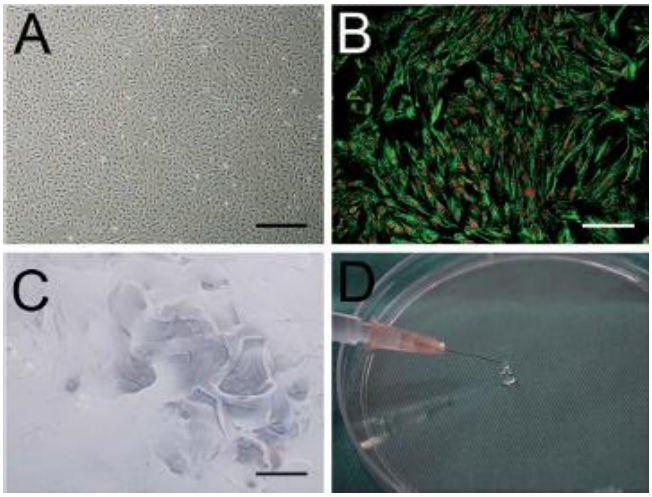


Figure 4. Microscopic observation of DMCs and injectable HAG scaffold. Optical microscopic observation of DMCs (A) and immunofluorescent staining of DMCs for vimentin (B). Optical microscopic observation of HAG microparticles (C) that could be injected (D) via a syringe (30G). Scale bars: 500 mm in A and C, 200 mm in B. Reprinted (adapted) with permission from Ref. [182].

Researchers have also explored chitosan in dentifrices and dental adhesives as antibacterial activity. In particular, Elsaka evaluated the antibacterial activity and bond strength of dental adhesives modified with various concentrations of chitosan. Adhesives with the lower concentrations of chitosan were more effective against *S. Mutans*. Moreover, a greater concentration of chitosan has negative effects on microtensile bond strength, the degree of conversion and pH [193]. Recently, more attention has been given to the use of chitosan combined with bioactive glass nanoparticles (CHT/BG-NP) in order to produce novel scaffolds for periodontium regeneration. These nanocomposites, due to their biocompatibility, effectively supported attachment and growth of cells, promoted the metabolic activity of human periodontal ligament cells and induced greater cell matrix mineralization [194]. Alginate is a high biocompatible linear copolymer composed of β-D-mannuronic acid and α-L-glucuronic acid linked by a 1–4 glycosidic bond commonly extracted from the cell wall of brown algae. Alginate forms spontaneous gels when exposed to divalent cations (e.g.,

Ca^{2+}). Such gel is used as a drug delivery device, wound healing dressing and tissue engineering scaffold [195]. Alginate is also available as composite systems in which it is associated with polyesters [196], polyethers [197], collagen [198] and chitosan [199] to effectively deliver drugs or proteins [200] and to form scaffolds composed of films, sponges, fibers, gels and freeze casted porous networks used in regenerative engineering [201]. Cellular adhesion on these devices is improved by side group modification of alginate with the RGD (Arg-Gly-Asp) peptides [202]. The most diffused use of alginate in dentistry is for periodontal regeneration. Moshaverinia et al. evaluated bone regeneration capacity of MSCs derived from the orofacial tissue. In particular, they compared periodontal ligament stem cells (PDLSCs) to gingival mesenchymal stem cells (GMSCs) both encapsulated in RGD (arginine-glycine-aspartic acid tripeptide)-modified alginate scaffold. Studies *in vitro* and *in vivo* showed that PDLSCs were able to repair the calvarial defects by promoting the formation of mineralized tissue, while GMSCs showed lower osteogenic differentiation capability [203]. Such device results particularly useful in oral and maxillofacial surgery. Similarly, nano-bioactive glass ceramic particle (nBGC) incorporated in alginate composite scaffold were able to increase alkaline phosphatase activity (ALP) of the human periodontal ligament fibroblast (hPDLF) cells seeded on these scaffolds [204]. Table 2 recaps the characteristics of the listed enzimatically degradable polymers.

Table 2. Enzymatically degradable polymers.

Materials	Classification	Dental application (Refs.)
Synthetic Polyethers	Synthetically-derived polyethers (PETH)	Coating on titanium dental implants [125]; Coatings on maghemite nanoparticles for treating dental hypersensitivity [126]; Hydroxyapatite disks with polydopamine-induced polyethylene glycol coating against a multi-species cariogenic biofilm [127]; Polyethylene glycol hydrogel with hydroxyapatite/tricalcium phosphate for guided bone regeneration procedures [128]; Poly(propylene glycol) as dental composites [129]; Self-etch adhesive system for the enamel based on acidic monomers of polypropylene glycol phosphate [130]; Pluronic F-127 hydrogels as scaffold for encapsulation of dental-derived mesenchymal stem cells [131]; Pluronic as drug delivery platform for the prevention and treatment of pathogenic plaque biofilms [132]
Proteins and Poly(Amino Acids)	Collagen	Scaffolds loaded with different growth factors for regenerating dental-pulp-like tissue [145]; Collagen-based barrier membranes for periodontal and implant therapy [146]; Collagen/fibrin microbeads as a delivery system for Ag-doped bioactive glass and DPSCs [147]
	Elastin	Scaffolds for osteogenic differentiation [152] and for the treatment of alveolar bone loss [153]
	Fibrin	Scaffold for dental pulp revascularization procedures [158]; Healing biomaterial scaffold for bone and soft tissue regeneration [159]; Device to promote periodontal wound healing and regeneration [160]

Continued on next page

Materials	Classification	Dental application (Refs.)
Proteins and Poly(Amino Acids)	Natural Poly(amino acids)	Polymeric calcium phosphate cements incorporated with poly-γ-glutamic acid [164]; Poly(L-lysine) coatings on titanium scaffolds [165]; Composites containing Poly(L-lysine) to prevent recurrent caries and restoration failures [166]
	Synthetic poly(amino acids)	Poly(L-glutamic acid) based compound for use in endodontic regeneration and for the treatment of dental inflammatory diseases [170]; Zinc-doped Portland-based resinous sealing cement linked with poly(aspartic acid) for dentine remineralization[171]
Polysaccharides	Hyaluronic acid (HA)	Hyaluronan gel for local application in surgery procedure [178] and in chronic periodontitis [179]; Restylane for endodontic treatment [180]; Hyaluronan scaffolds for regenerative procedure [181]; Injectable tissue engineering composite of hyaluronic acid gel, tooth bud-derived dental mesenchymal cells and transforming growth factor-b1 [182]
	Chitosan (CS)	Chitosan pellicles for the study of bacterial adhesion [191]; Chitosan nanoparticles as drug carriers to enhance antibacterial effect [192]; Chitosan-based dental adhesives [193]; Chitosan combined with bioactive glass nanoparticles (CHT/BG-NP) for periodontium regeneration [194]
	Alginate	RGD (arginine-glycine-aspartic acid tripeptide)-modified useful in oral and maxillofacial surgery [203]; Nano bioactive glass ceramic particles (nBGC) incorporated in alginate composite scaffold for periodontal tissue regeneration [204]

4. Regulatory aspects of the clinical application of biopolymers

The use of biopolymers in dental practice is specified in various regulatory requirements and directives. One such regulation is the new Medical Device Regulation (EU) 2017/745 for Medical Devices, which came into force on May 25th 2017, replacing the former EU Directive 93/42/EEC. These requirements relate to safety, quality and suitability. Moreover, it is expressly required special attention to the choice of materials being used. This is especially true when considering the toxicity and mutual compatibility with tissues, cells, body fluids, and other used materials. The intended use of the medical device must always be considered in this process. Then, manufacturers of medical products tend to select polymers for their applications certified for biocompatibility. A similar process is valid in the US were the FDA produced a regulatory amendment [205].

5. Conclusions

The application of biodegradable polymers in dental practice widely improved the clinical response of patients. This is because biodegradable polymers can be utilized as eternal or temporary prosthesis thanks to their ability to break down and be absorbed by the body without producing harmful degradation products. Moreover, they offer great potential for controlled drug delivery,

wound management, dental restorations, and tissue engineering. However, the further development of the biodegradable polymers, especially in the regeneration field, requires deeper knowledge on basic tissue biology and molecular mechanisms of tissue turnover at different periods of human life and in different diseases. Without any doubt, this investigation will be the guiding thread of dental research in the next future.

Conflicts of interest

There is no conflict to declare.

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Author contribution

Raffaele Conte, Anna Di Salle and Orsolina Petillo planned, write and revised the paper. Francesco Riccitiello, Gianfranco Peluso and Anna Calarco planned and revised the article.

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